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PROFILES IN GU ONCOLOGY

Yasser M. A. Ged, MB BS



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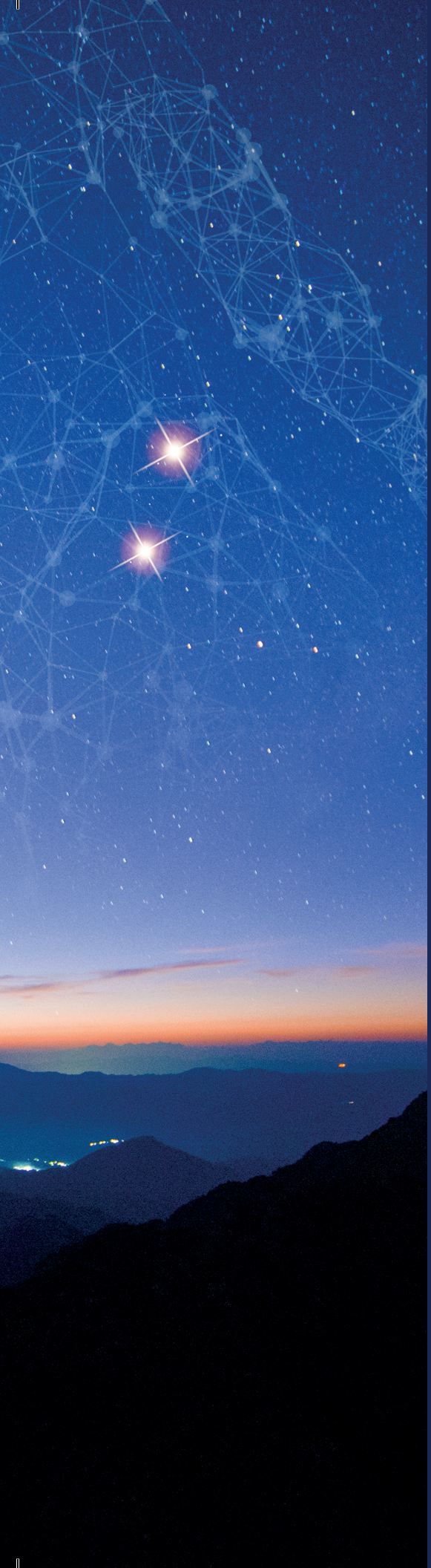
Illuccix® for the preparation of ^{68}Ga-PSMA-11 is poised to expand the potential of PSMA PET imaging and help guide more informed management decisions in prostate cancer.[1-4]



References: 1. Illuccix (kit for the preparation of gallium Ga 68 gozetotide injection) prescribing information. **2.** Massat MB. Nuclear medicine prepares for greater 68Ga demand. *Appl Radiol.* 2021;50(2):30-31. https://appliedradiology.com/articles/nuclear-medicine-prepares-for-greater-ga-68-demand. Accessed July 13, 2021. 3. Velikyan I. 68Ga-based radiopharmaceuticals: production and application relationship. *Molecules.* 2015;20(7):12913-12943. 4. ARTMS and Telix Pharmaceuticals announce successful production of PSMA-11 with cyclotron produced 68Ga from a solid target [news release]. Telix Pharmaceuticals; January 12, 2021. https://telixpharma.com/news-media/artms-and-telix-pharmaceuticals-announce-successful-production-of-68ga-psma-11-with-cyclotron-produced-68ga-from-a-solid-target/.

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- with suspected metastasis who are candidates for initial definitive therapy
- with suspected recurrence based on elevated serum prostate-specific antigen (PSA) level

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Risk for Misdiagnosis
Image interpretation errors can occur with gallium Ga 68 gozetotide PET. A negative image does not rule out the presence of prostate cancer and a positive image does not confirm the presence of prostate cancer. The performance of gallium Ga 68 gozetotide for imaging of biochemically recurrent prostate cancer seems to be affected by serum PSA levels and by site of disease. The performance of gallium Ga 68 gozetotide for imaging of metastatic pelvic lymph nodes prior to initial definitive therapy seems to be affected by Gleason score. Gallium Ga 68 gozetotide uptake is not specific for prostate cancer and may occur with other types of cancer as well as non-malignant processes such as Paget's disease, fibrous dysplasia, and osteophytosis. Clinical correlation, which may include histopathological evaluation of the suspected prostate cancer site, is recommended.

Radiation Risks
Gallium Ga 68 gozetotide contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Ensure safe handling to minimize radiation exposure to the patient and health care workers. Advise patients to hydrate before and after administration and to void frequently after administration.

ADVERSE REACTIONS

The safety of gallium Ga 68 gozetotide was evaluated in 960 patients, each receiving one dose of gallium Ga 68 gozetotide. The average injected activity was 188.7 ± 40.7 MBq (5.1 ± 1.1 mCi). No serious adverse reactions were attributed to gallium Ga 68 gozetotide. The most commonly reported adverse reactions were nausea, diarrhea, and dizziness, occurring at a rate of < 1%.

DRUG INTERACTIONS

Androgen deprivation therapy and other therapies targeting the androgen pathway Androgen deprivation therapy (ADT) and other therapies targeting the androgen pathway, such as androgen receptor antagonists, can result in changes in uptake of gallium Ga 68 gozetotide in prostate cancer. The effect of these therapies on performance of gallium Ga 68 gozetotide PET has not been established.

You are encouraged to report suspected adverse reactions of prescription drugs to the FDA.

Please note this information is not comprehensive. Please see brief summary of the full prescribing information on the next page, or visit illuccixhcp.com for full prescribing information.

Illuccix (kit for the preparation of gallium Ga 68 gozetotide Injection)
BRIEF SUMMARY: Consult the full prescribing information for complete product information

WARNINGS AND PRECAUTIONS

Risk for Misdiagnosis
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ADVERSE REACTIONS

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of ILLUCCIX has been established based on studies of another formulation of gallium Ga 68 gozetotide in patients with prostate cancer [see Clinical Studies (14)]. Below is a display of the adverse reactions in these studies. The safety of gallium Ga 68 gozetotide was evaluated in 960 patients, each receiving one dose of gallium Ga 68 gozetotide. The average injected activity was 188.7 ± 40.7 MBq (5.1 ± 1.1 mCi). No serious adverse reactions were attributed to gallium Ga 68 gozetotide. The most commonly reported adverse reactions were nausea, diarrhea, and dizziness, occurring at a rate of < 1%.

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USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
ILLUCCIX is not indicated for use in females. There are no available data with gallium Ga 68 gozetotide injection use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. All radiopharmaceuticals, including ILLUCCIX, have the potential to cause fetal harm depending on the fetal stage of development and the magnitude of the radiation dose. Animal reproduction studies have not been conducted with gallium Ga 68 gozetotide.

Lactation

Risk Summary
ILLUCCIX is not indicated for use in females. There are no data on the presence of gallium Ga 68 gozetotide in human milk, the effect on the breastfed infant, or the effect on milk production.

Pediatric Use

The safety and effectiveness of gallium Ga 68 gozetotide in pediatric patients have not been established.

Geriatric Use

The efficacy of gallium Ga 68 gozetotide PET in geriatric patients with prostate cancer is based on data from two prospective studies [see Clinical Studies (14)]. Most patients in these trials were 65 years of age or older (72%). The efficacy and safety profiles of gallium Ga 68 gozetotide appear similar in younger adult and geriatric patients with prostate cancer, although the number of younger adult patients in the trials was not large enough to allow definitive comparison.

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Trends in the Management of Advanced and Metastatic Prostate Cancer

Daniel Tennenbaum, MD interviews Catherine H. Marshall, MD



Catherine H. Marshall, MD, MpH

PROSTATE CANCER IS the third most common cancer overall, and the most common in men, within the US. Great clinical gains have been made in the management of advanced prostate cancer, but metastatic prostate cancer remains incurable and carries significant morbidities in its clinical symptomatology and the side effects of managing the disease. As clinicians pursue further advances in the management of prostate cancer, the fusion of multimodal therapy continues to gain traction. Catherine H. Marshall, MD, MPH, an assistant professor of oncology at the Johns Hopkins University School of Medicine, was recently interviewed by Daniel Tennenbaum, MD to help clarify the recent trends in management of advanced and metastatic prostate cancer. More specifically, she discussed when, as a medical oncologist, she utilizes radiation therapy in the management of advanced prostate cancer.

Dr. Tennenbaum: Today, we're going to talk about how and when you, as a medical oncologist, incorporate radiation into the management of men with metastatic prostate cancer. As a point of introduction, when do medical oncologists typically get involved in the management of prostate cancer? As a urology resident, I can't help but think that for localized disease, it's either the urologist or the radiation oncologist who is usually "at the front lines," and that the medical oncologist will come in to provide adjuvant therapy or treatment of advanced or metastatic disease. Is that something you would agree with?

Dr. Marshall: Yes, that's definitely something that I would agree with. Obviously, most prostate cancer, when it gets diagnosed in this country, is diagnosed when it's still local. Usually, medical oncologists do not see those patients. There are some patients with very high-risk prostate cancer who are getting androgen deprivation therapy (ADT) and abiraterone, so some of those patients, I see for the administration of their systemic therapy. For the most part, the patients I see are men who have metastatic disease, or who have disease recurrence after localized treatment, which we refer to as biochemical recurrent disease.

And when you say 'metastatic disease', obviously not all metastatic prostate cancer is created equally. Can you please elaborate on hormone-sensitive versus hormone-refractory metastatic prostate cancer, as well as the concept of metastatic versus nonmetastatic hormone-refractory disease?

There are probably 3 categories I would say. (1) non metastatic, meaning disease is not visible on scans. Traditionally, we use conventional CT and NM bone scans to define this but can use PSMA PET/CT too; (2) oligometastatic disease, meaning that there is some disease that is visible but there are only a few areas of disease; (3) metastatic disease, meaning it is apparent on scans. Again, traditionally, we use CT and NM bone scan to define this.

Regarding whether the disease is considered hormone sensitive or hormone refractory, it is just relative to whether or not the patient has been treated with androgen deprivation therapy. Usually, at initial cancer diagnosis, when a patient has not been exposed, nor has the cancer been exposed to any androgen deprivation therapy, we consider that to be hormone naive. If the disease progresses despite having castrate levels of testosterone, then that's when we consider the disease to be hormone refractory, meaning that it's growing despite the castration levels of testosterone.

At what point do you start to consider incorporating radiation therapy (RT) into the treatment of your metastatic patients? Is RT something you would use up front for local control? Are you using it for adjuvant therapy?

For patients who present with de novo metastatic disease, where their first presentation of prostate cancer is metastatic, and if they have significant lower urinary tract symptoms, then sometimes I'll refer these men for radiation just because of the therapeutic and symptomatic benefit. Additionally, for patients who have low-volume metastatic disease, there's benefit to considering radiation to the prostate for those patients in conjunction with systemic therapy.

On the other hand, for the patients who have recurrence of their disease after local treatment, there may still be a role for salvage radiation. This is when there's a biochemical recurrence and the radiation gets delivered to the postprostatectomy prostatic bed, and sometimes pelvic lymph nodes.

With PSMA imaging, or even conventional imaging, we are

now sometimes identifying oligometastatic disease that may be amenable to radiation. If patients have recurrent disease, and we identify oligometastatic disease, then sometimes I will refer those patients to radiation oncology to see about getting radiation to the sites of oligometastatic disease.

What about for patients who don't have oligometastatic disease but rather have symptomatic metastatic disease? Bone lesions are the obvious circumstance to consider, of course. Is SABR an option for symptomatic metastatic disease?
Yes, it absolutely is. Sometimes, those patients will get conventional radiation, external-beam radiation therapy (EBRT) or SBRT, but radiation is definitely used in the palliation of symptoms. Though this usually doesn't come up in hormone-sensitive disease, it certainly can. We do see that in more advanced disease of course.

Got it. With all that being said, what kind of benefit are we seeing with the use of radiation in patients who have already been diagnosed with metastatic disease?
The benefits really depend on the different contexts. In treatment to the primary tumor for low-volume metastatic disease, subset analysis of the STAMPEDE trial showed an overall survival benefit. In the other studies we've spoken about, you're really looking at the progression-free survival as the largest benefit to the patient, trying to delay the time to initiation of hormone therapy. That's usually what I talk to my patients about, extending time to disease progression.

Moving back to what you were mentioning earlier, using EBRT for low-volume local control. In our discussion prior to this interview, you mentioned the Journal of Clinical Oncology article by Rusthoven et al, "Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer." One aspect of that article I found interesting was its suggestion that cytoreduction of some form may have clinical benefit in the metastatic prostate cancer setting. From my previous understanding, that's a somewhat controversial position.
Yes. The HORRAD trial was an older study which did not show a benefit. However, patient selection is key. In the STAMPEDE study, subset analysis showed benefit in patients with low volume metastatic disease. A meta-analysis of the two trials for men with low-volume disease showed benefit. So for patients with low-volume metastatic disease, I usually refer to radiation oncology for a discussion about adding in radiation.

We've seen in the last number of years a step toward bringing therapies that were offered later in disease courses earlier and earlier, particularly for prostate cancer. Do you foresee a future where conjunctive systemic therapy and radiation are offered even in just localized disease?
Yes, and some of that is already happening now. With very high-risk prostate cancer, abiraterone is now being used in that setting, too. It started out with radiation, and then radiation and ADT, and now radiation, ADT, and abiraterone for a short period of time, and then stopping all those therapies. In oligometastatic disease, initially we would not use both hormone therapy and radiation, and now we have trials combining SBRT plus with other therapies as well. The ultimate goal is to figure out what the best treatment is for each individual patient, and we obviously still have a way to go toward figuring that out. Who really needs more intensification of treatment versus maybe de-escalation of treatment for others?

When you mention individualizing patient care, are there any subsets of patients—whether it be by age, family history, or race—that are responsive to radiation therapy when you're already putting them on systemic therapy?
Well, I think we will find that there probably are some subsets of prostate cancer, again, probably related to more aggressive disease, where there's going to be more micrometastatic disease that you're not targeting. The patients who are more likely to have that are probably going to be the ones who are less likely to benefit from this localized approach.

Lastly, I like to ask everyone we interview this question: What does the future hold for the management of men with metastatic prostate cancer?
I think the future of managing metastatic prostate cancer is going to be dramatically different in the next 20 years. Recent trials have helped us realize that there are definitely some patients who need an escalation of therapy and more therapy up front, and I think the reverse will be true, too. We will find that some patients can afford a de-escalation of therapy and less therapy. I think, as we will continue to identify new targets and new therapies, that will be successful against those targets.

Will there be any further implementation of immunotherapy in prostate cancer?
I think so. I definitely think so. Whether, again, that will be new targets or different combinations, I think we will figure out immunotherapy in prostate cancer.

References:
https://pubmed.ncbi.nlm.nih.gov/36001857/ - STOMP and ORIOLE; https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1003998 - STAMPEDE

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Daniel Tennenbaum is a urology resident at Maimonides Medical Center in Brooklyn, NY. His interests include surgical education and GU oncology with a focus on pediatric malignancies.

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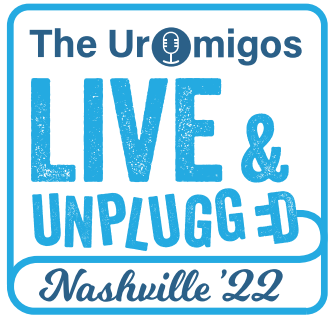
Michael R. Page, PharmD, RPh







IN A ONE-OF-A-KIND EVENT, The Uromigos Live & Unplugged convened global thought leaders in the care of urologic malignancies to examine the current state of disease management, share contrasting views on therapeutic strategies, and predict the future of bladder cancer, prostate cancer, and renal cell carcinoma. Over the course of 1.5 days, the program incorporated gamified presentations and live and in-depth discussions to facilitate new clarity in the field of urologic malignancies. Transcending the confines of a typical meeting, this live event ensured active discussion through multiple channels, including live social media polls, live and remote audience member Q&A, and social media comments integrated directly into the content. Experts challenged each other to generate unique content that could not be reached through any other meeting format.



The meeting, co-hosted by **Thomas Powles, MBBS, MRCP, MD,** professor of genitourinary oncology at the University of London and director of the Barts Cancer Centre, and **Brian Rini, MD,** medical oncologist at Vanderbilt Health in Nashville, Tennessee, builds on the success of the weekly Uromigos podcast developed by Drs. Powles and Rini. Regarding the unique format, Dr. Rini, noted, "We set out to create high-quality content through an unconventional approach to limit the didactics and slides and build on our podcast format through panel-based conversations of standard approaches, controversies, and novel drugs relevant to the clinical care of genitourinary cancer patients."

Bladder cancer

In the frontline setting of urothelial cancer management, multiple checkpoint inhibitor trials—including IMvigor130, DANUBE, KEYNOTE-361, CheckMate-901, and Nile—have failed to show a significant benefit in improving overall survival.[1] "We have learned that the frontline combinations in metastatic urothelial cancer have not been successful," said moderator Dr. Powles.

Urologic oncologists are looking to combination data for antibody-drug conjugates with checkpoint inhibitors as a way forward. For example, enfortumab vedotin plus pembrolizumab may be a promising combination in the treatment of patients with urothelial carcinoma who are ineligible for platinum-based chemotherapy.[2] According to Dr Powles, "Enfortumab vedotin plus pembrolizumab is likely to change practice with ongoing trials like EV-302." However, at present, chemotherapy remains the standard frontline therapy.

In the adjuvant setting, positive results have been reported, with nivolumab improving disease-free survival in the CheckMate-247 clinical study.[3] However, a non-prespecified subgroup analysis found that results were less promising in patients with upper-tract urothelial cancer. Consequently, some urologic oncologists choose gemcitabine plus cisplatin as a treatment of choice over nivolumab, but this practice is controversial. Regarding the results of CheckMate-247, Matthew Galsky, MD, of the Mount Sinai School of Medicine, thinks that "clinical trials are designed to answer a specific question, and this trial asked whether adjuvant nivolumab improved overall survival in the all-comer population and whether it improved disease-free survival in tumors harboring high levels of [programmed death ligand 1 (PD-L1)] expression. Both primary analyses were positive," Dr. Galsky said, "We should not be relying on subgroup analyses to guide these clinical decisions."

Though trials regarding checkpoint inhibitors were negative in the frontline setting, oncologists are hopeful about the potential for antibody-drug conjugates in combination with checkpoint inhibitors. Prior biomarkers like PD-L1 expression were disappointing in terms of interobserver reliability, but a new generation of biomarkers in bladder cancer is emerging. "The second generation of biomarkers looks exciting, with [circulating tumor DNA] and [tumor mutation burden] being the most promising," Dr Powles said. Such biomarkers may help select patients who are most likely to benefit from therapy, informing care and improving outcomes over the next 5 years and beyond.

Prostate cancer

In the current management of metastatic hormone-sensitive prostate cancer (mHSPC), appropriately identifying patients who are candidates for triplet therapy with dual androgen deprivation therapy (ADT) and docetaxel is a major challenge. Additionally, the ideal sequence of treatment remains unclear.[4] Tolerability challenges with docetaxel have led some groups to study alternative, and potentially more tolerable, chemotherapy with cabazitaxel. "One study that I think we need to be thinking about is a study of ADT plus docetaxel versus ADT plus cabazitaxel, with everyone getting [novel hormonal therapy] background therapy," said Christopher Sweeney, MBBS, of the Dana-Farber Cancer Institute. Noting the tolerability and adherence challenges, Dr. Sweeney said, "We struggle



The Prostate Cancer Panel presenting.

with getting people to use docetaxel, but could we get people to use cabazitaxel in the up-front setting?" Asking such questions is important for moving the field of prostate cancer management forward and for clarifying optimal patterns of care.

Advanced imaging modalities in prostate cancer have changed treatment paradigms and created uncertainties in management. As novel imaging enables identification of metastatic disease earlier than was previously possible, the population of patients with metastatic disease identified today is different from the population studied with treatments to manage metastases. These changes are concurrent with novel metastasis-directed therapies such as poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors and anti-prostate-specific membrane antigen (PSMA) therapies,[5,6] adding further complexity to the optimal sequencing of treatment. Ongoing trials are underway and will hopefully provide clarity. According to Rana McKay, MD, a medical oncologist at the University of California, San Diego Moores Cancer Center, "There is a series right now of phase 3 trials that are currently ongoing in the metastatic hormone-sensitive space introducing PSMA-based therapy for PSMA-positive disease, PARP inhibition for biomarker-positive disease, AKT inhibition for people with PTEN loss, and also looking at CDK4/6 inhibition in this setting." Commenting on the importance of these upcoming trial results, Dr. McKay noted, "They are likely to change the whole paradigm of what we do in mHSPC."

"They are likely to change the whole paradigm of what we do in mHSPC." –Dr. Rana McKay

Despite excitement about the forthcoming results, experts differ on the future of prostate cancer management. "In 2027, I think we are going to be dividing the disease of prostate cancer into synchronous and metachronous disease and into patients that we can treat with metastasis-directed therapy and the rest," said Nick James, MBBS, PhD, FRCP, FRCR, of the Institute of Cancer Research, London. However, other experts are more optimistic about further development of





Left: Dr, Daniel George and Christopher Sweney

Above: Dr Kala Sridhar and Dr. Shilpa Gupta

biomarkers to inform management. Daniel George, MD, of the Duke University School of Medicine, believes "the current therapies available today will be more prevalent in our practice in mHSPC populations, including novel androgen receptor-targeting therapies and docetaxel chemotherapy, but I think what is going to change is our assessment of frontline patients. We are going to be doing as a standard not just bone scans and [computed tomography] scans, but we are also going to be testing for PSMA and doing much more standard genetic testing—both germline and somatic." De-escalation of therapy is also on the horizon. Neeraj Agarwal, MD, of the Huntsman Cancer Institute at the University of Utah, said "By 2027, the median survival of patients with mHSPC will approach 10 years, and we will be emphasizing de-escalation of therapy and maintaining quality of life for our patients."

Renal cell carcinoma

The present management of renal cell carcinoma (RCC) in the frontline setting comprises multiple potential combinations, including single-agent immunotherapy, immunotherapy combinations, and targeted agents in combination with immunotherapy. However, most experts agree that ipilimumab in combination with nivolumab may be the most appropriate choice for most patients in the frontline setting.[7,8]

Although results of the COSMIC-313 clinical trial evaluating cabozantinib plus ipilimumab/nivolumab showed positive results in improving progression-free survival in frontline disease, subgroup analyses showed that the benefits of therapy are concentrated in intermediate-risk patients, with little improvement in outcomes in poor-risk patients.[9] As a result, some clinicians are unsure of how to incorporate a triple therapy regimen and continue to support doublet IO-based combination therapy as the standard of care. However, continued development is welcomed by oncologists. Tian Zhang, MD, of the University of Texas Southwestern Medical Center, noted, "We have a great number of active immunotherapy-based combinations in RCC in the frontline setting approved for our patients." With a wealth of options available, Dr. Zhang emphasized the importance of individualizing therapy for each patient. "Certainly, thinking about patient characteristics, and comorbidities, allows us to select the right approach," she said.

Renal cell carcinoma management developments include advances in treatments targeting multiple novel pathways such as hypoxia-inducible factor-2 alpha (HIF-2α) and CD70 receptors.[10-13] David McDermott, MD, of the Beth Israel Deaconess Medical Center, expressed enthusiasm for HIF-2α targeting in particular. "The fact that we are seeing activity shows that HIF2 is an



(L-R) Dr. Brian Rini, Dr. Michael Morris, Dr. Nick James, Dr. Daniel George, Christopher Sweeney, MBBS, Dr. Thomas Powles, Dr. Rana McKay, Dr. Neeraj Agarwal.

important target," he said. Specifically, recent positive data indicate single-agent activity with the HIF-2α inhibitor belzutifan ranging from 25% to 31% across study arms, with response rates as high as 57% when used in combination with cabozantinib.[10,11] Regarding these results, Dr. McDermott noted, "Belzutifan has activity and a very favorable toxicity profile, but we are seeing activity in a subset of patients. The activity is delayed, but in the patients who benefit, it is often prolonged." He encouraged a path of development that focuses on the patients most likely to benefit rather than the conventional approach of initiating therapy in the later-line settings and slowly moving to earlier-line settings. "Let's identify those tumor markers to predict who will benefit and then move HIF inhibition up sooner. And there are other combinations we can use to build on this success for patients who are not likely to benefit from an immune checkpoint inhibition strategy." Innovative clinical trial strategies focusing on biomarkers that predict which therapies are optimal for specific patient groups will inform optimal management of renal cell carcinoma in the future.

"We accomplished our goals and can build on this format moving forward to further innovate and change the face of medical education." –Dr. Brian Rini

Conclusions

The Uromigos Live & Unplugged event provided a unique forum for integrating the perspectives of multiple global experts in a live format to inform both the current state and future of management across urologic malignancies. With multiple exciting developments incorporating novel mechanisms, biomarkers for selection of targeted therapy, and innovative treatment approaches, clinicians can look forward to continued progress in the management of patients with bladder cancer, prostate cancer, and renal cell carcinoma. Through innovative, engaging, and entertaining live events such as The Uromigos Live & Unplugged, more clinicians can gain a clear understanding of both the state-of-the-art and future directions in care for the benefit of their patients.

According to co-host Dr. Brian Rini, following the event, "We accomplished our goals and can build on this format moving forward to further innovate and change the face of medical education."

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(L-R) - Dr Thomas Powles, Dr. David McDermott, Dr. Axel Bex, Dr. Tian Zhang Dr. Brian Rini, Dr. Sumanta Pal.

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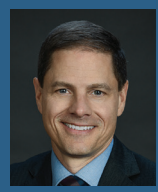
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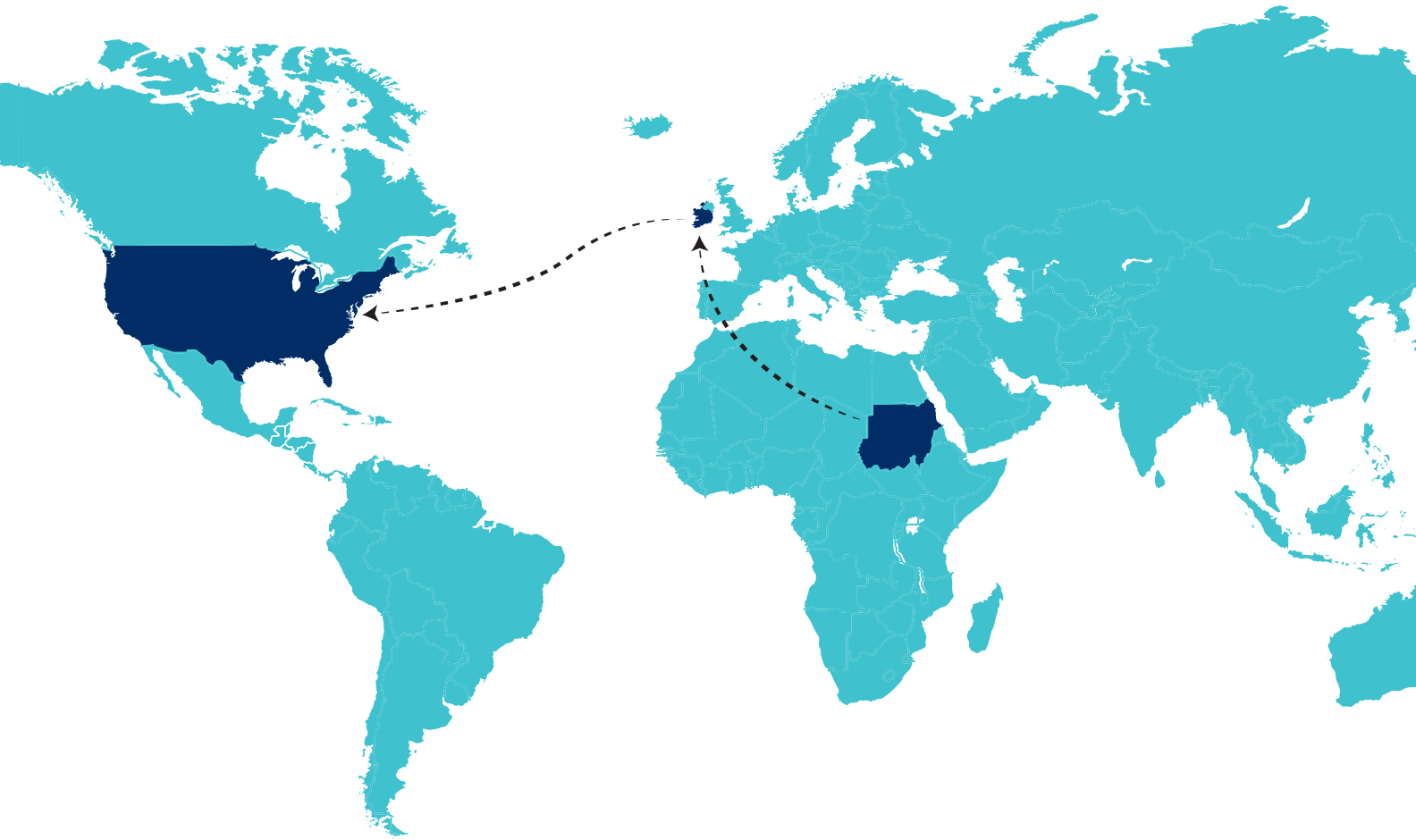
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Broadcasting the latest developments in GU cancer



Brian Rini, MD





Yasser M. A. Ged, MB BS–

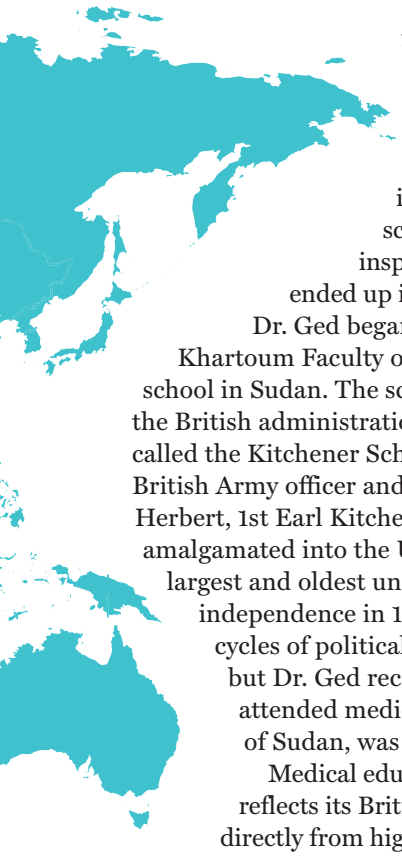
A Career Pathway Extending Over Three Continents

Dr. Yasser Ged describes how he began his medical training in Sudan, how he committed to oncology in Ireland, and how he realized his goal to specialize in genitourinary oncology, focusing on kidney cancer, at Johns Hopkins Medicine in the US.

Linda Brookes, MSc

DR. YASSER GED has come a long way, both figuratively and literally in his career journey, starting with his studies in North Africa, then traveling to Europe for his postgraduate training, and finally moving to the US to advance his career in genitourinary oncology. Today he practices in medical oncology and serves as Co-Director, of the Kidney Cancer Research Program at Johns Hopkins Medicine, and Assistant Professor of Oncology at Johns Hopkins University in Baltimore.

That Dr. Ged was able to move from his home country, Sudan, and adjust so successfully to working overseas was in large part facilitated by his father, who played a big role in helping and advising him during his career, he explains. His family lived by the country's main seaport, Port Sudan, on the Red Sea, where his father worked as a shipping captain. "My father had had the options of going into medicine or marine studies, but opted to study for a degree in marine law and he was successful in this



field," he recalls. "He inspired me along my pathway and advised me about my career since I was young," he acknowledges. In high school, Dr Ged excelled in science, "so with my love of science, particularly biology, and inspiration from my dad, that's how I ended up in medicine," he relates.

Dr. Ged began his studies at the University of Khartoum Faculty of Medicine, the oldest medical school in Sudan. The school opened in 1924, during the British administration of Sudan and was originally called the Kitchener School of Medicine (after senior British Army officer and colonial administrator, Horatio Herbert, 1st Earl Kitchener). In 1951, the school was amalgamated into the University of Khartoum, the largest and oldest university in Sudan. Since gaining independence in 1956, Sudan has experienced cycles of political instability and economic crises, but Dr. Ged recalls that during the time he attended medical school, Khartoum, the capital of Sudan, was relatively calm.

Medical education at Khartoum in part reflects its British origins in that students enter directly from high school and, after successfully completing 6 years, are awarded the MB BS (Bachelor of Medicine, Bachelor of Surgery) degree. Dr Ged gained his MB BS in 2005, graduating in the top 10 of his class, and went on to an internship in internal medicine at Al Jawda Hospital in central Khartoum. Then, taking advantage of the Faculty's connections with European and US professional institutions, Dr. Ged chose Ireland as the location for his residency, which he began, under the auspices of the Royal College of Physicians of Ireland, in 2009. His rotation took him to many parts of the country, including Dublin, Galway, Waterford, and Limerick. Adjusting to Western culture wasn't very difficult, he says, "I used to go abroad to conferences, but also since my dad was a shipping captain we used to travel a lot with him to Europe. So adapting to the culture was kind of easy."

While trying to decide whether to specialize in oncology, rheumatology, or pulmonology, he did 6 months of training in rheumatology. "I didn't think that was for me, so I changed to oncology and I loved it!" he recalls. During his oncology rotation, he became interested in genitourinary cancers, in particular kidney cancer. "I saw an interesting case where a patient with stage IV kidney cancer underwent a spontaneous resolution of metastatic disease after nephrectomy, which only happens once in a thousand cases," he recollects. "I became intrigued about kidney cancer and that's why I wanted to pursue a career in genitourinary cancer and focus on that." Before he left Ireland, he gained his Certificate of Completion of Specialist Training (CCST):and board certifications from the Royal College of Physicians Medicine (Ireland) in internal medicine (2011) and oncology (2017). Dr Ged speaks of Ireland fondly. "I still have many friends there," he says, He also retains a love of Irish music and rugby football.

He decided on a Fellowship in the US and in 2019 began an Advanced Medical Oncology Fellowship at Memorial Sloan-Kettering Cancer Center (MCKCC) in New York, focusing on genitourinary oncology, mainly clinical training and research in kidney cancer. There, he met kidney cancer pioneer Robert J Motzer, MD Section Head, Kidney Cancer, Genitourinary Oncology Service; Jack and Dorothy Byrne Chair in Clinical Oncology. "I had been reading his work and then I ended up actually working with him and training under him," Dr. Ged recollects. Another mentor was Martin H. Voss, MD, Clinical Director of the MSKCC Genitourinary Medical Oncology Service. Working in the US turned out to be a very happy experience and Dr. Ged decided to stay. "I love the way the cancer research goes in the US and the hybrid in academia of caring for patients and developing research," he says. He points out that he is just one of a number of Sundanese-born physicians pursuing successful careers in the US.

"I love the way the cancer research goes in the US and the hybrid in academia of caring for patients and developing research." –Dr. Yasser Ged

In 2020 Dr Ged moved to Johns Hopkins, where most of his clinical practice is focused on kidney cancer and the remainder on testicular cancer, seeing patients at the Skip Viragh Outpatient Cancer Center in Baltimore. He co-directs the Kidney Cancer Research Program with Nirmish Singla, MD, MSc, Assistant Professor of Urology and Oncology in the Brady Urological Institute and Director of Translational Research in Genitourinary Oncology. Their projects are mainly focused on three areas: furthering the understanding the biology of kidney cancer; studying biomarkers for clinical efficacy of specific interventions, primarily immunotherapy. and therapeutics-based clinical trials and preclinical studies.

Dr. Ged has recently acted as site principal investigator (PI) for a number of clinical trials, including CONTACT-03 (NCT04338269), which investigated

atezolizumab combined with cabozantinib versus cabozantinib alone after immune checkpoint therapy in patients with advanced kidney cancer.[1] "We expect the results to CONTACT-03 to be out next year," Dr. Ged predicts. He is also site PI for LITESPARK-022 (MK-6482-022) (NCT05239728), a phase 3 study of pembrolizumab combined with belzutifan or placebo as adjuvant treatment of clear cell renal cell carcinoma (ccRCC),[2] and PROSPER RCC/EA8143, a Phase 3 study that compared priming the immune system with neoadjuvant nivolumab prior to nephrectomy, followed by adjuvant nivolumab in patients with high-risk RCC compared to surgery alone. Late-breaking data from the trial were presented during the 2022 congress of the European Society for Medical Oncology (ESMO).[3]

Dr. Ged has been interested in the effects of COVID-19 and is site PI for the natural history study, NCCAPS (NCI COVID-19 in Cancer Patient, NCT04387656), which is investigating the effects of COVID-19 on cancer patients. Researchers are collecting blood samples, medical information, and medical images from nearly 1800 cancer patients who also had COVID-19 and aim to follow them for up to 2 years. An initial report after 2 months of complete follow-up was presented at the 2021 American Society of Clinical Oncology (ASCO) annual meeting.[4] Dr Ged is also responsible for site enrollment in the ODYSSEY RCC (Outcomes Database to prospectivelY aSSEss the Changing TherapY Landscape in Renal Cell Carcinoma trial NCT04919122) a prospective, observational phase 4 study to understand the cancer management and health-related quality of life in patients with metastatic RCC in routine real-world US clinical practice, including both community and academic treatment settings. "We actually have the highest enrollment in the country to date," Dr. Ged notes. The upcoming randomized S2200 study, PAPMET2 (NCT05411081), a phase 2 trial sponsored by the National Cancer Institute and led by SWOG, will compare cabozantinib alone or with atezolizumab in patients with papillary metastatic RCC.

Dr. Ged recently initiated a pilot study looking at combined aerobic and resistance exercise with immunotherapy in patients with metastatic RCC (NCT05103722). The trial will investigate effects on quality of life, changes in physical activity levels, and the change in inflammatory myokines with the exercise intervention. The reason for this study, Dr. Ged explains, is that during one of his research studies at MSKCC, they found that patients with sarcopenia (weak muscles) did poorly when they were treated with immunotherapy, "There are some preclinical data to show that exercise can affect T cell activity and can enhance immunotherapy activity," he adds. "So we are selecting kidney cancer patients who have a more sedentary lifestyle and would be expected to have weak muscles, and we are going to look at whether there is any hint of activity that exercise could influence immunotherapy outcomes or not."



Dr. Ged enjoying a light moment outside work.

Apart from research and clinical practice, Dr. Ged's other roles at Johns Hopkins include mentoring Fellows and promoting diversity in clinical trial enrollment. "I am the Johns Hopkins Equity Officer in one of the NCI grants," he explains. "This is one of my interests in the field and it is a challenge everywhere," he notes. "It should be made easier by using social media platforms, but implementation still needs a lot of effort. But right now, we have a lot of tools that we can incorporate to understand how better to promote it," he asserts. Outside Johns Hopkins, Dr Ged's professional activities involve serving as site representative on the National Comprehensive Cancer Network (NCCN) panel for kidney cancer. (The latest version of the guideline was issued September 22, 2022.[5])

Away from medicine, Dr. Ged admits to being a music fan and a vinyl record collector. "I have about 2000 records so far," he admits, and he travels to record shows across the country to add to his collection. His taste in music is broad, spanning rock and roll to electronic. He still keeps in touch with Sudan, although his closest relatives now live abroad, his mother and one sister in Cambridge, UK, and another sister in Ireland. The rest of the family remains in Sudan, and under current unstable conditions, most contact with them is online, Dr. Ged says.

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1L aRCC

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)



EFFICACY IN BALANCE[1]

CABOMETYX + OPDIVO brings together efficacy, safety, and tolerability data for your 1L aRCC patients[1]

1L aRCC treatment that offers a balance of data:
superior OS, safety and tolerability,
and patient-reported quality of life[1-4] *

A BALANCE OF DATA*



*Superior OS vs sunitinib in patients with previously untreated aRCC. Primary analysis OS results: 40% reduction in risk of death with CABOMETYX + OPDIVO vs sunitinib (HR=0.60; 98.89% CI: 0.40-0.89; *P*=0.001); median OS was not reached in either arm. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown.[1,2]

1L=first-line; aRCC=advanced renal cell carcinoma; CI=confidence interval; FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index 19; HR=hazard ratio; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

INDICATIONS

CABOMETYX® (cabozantinib), in combination with nivolumab, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX is indicated for the treatment of patients with advanced RCC.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hemorrhage: Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in RCC, HCC, and DTC studies. Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

Perforations and Fistulas: Fistulas, including fatal cases, occurred in 1% of CABOMETYX patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX patients. Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

Thrombotic Events: CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism in 2% of CABOMETYX patients. Fatal thrombotic events occurred in CABOMETYX patients. Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

Hypertension and Hypertensive Crisis: CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX patients. Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Please see additional Important Safety Information throughout and Brief Summary of the Prescribing Information for CABOMETYX on following pages.

Superior PFS and ORR results in the ITT population in the primary analysis[1]

Median follow-up time of 18.1 months; range: 10.6-30.6 months[2]

Primary endpoint

MEDIAN PFS WAS DOUBLED[1]*

16.6 months CABOMETYX + OPDIVO (95% CI: 12.5-24.9; n=323)

vs

HR=0.51 (95% CI: 0.41-0.64) *P*<0.0001

8.3 months sunitinib (95% CI: 7.0-9.7; n=328)

Secondary endpoint

ORR WAS DOUBLED[1]*

55.7% CABOMETYX + OPDIVO (95% CI: 50.1-61.2; n=323)

vs

P<0.0001

27.1% sunitinib (95% CI: 22.4-32.3; n=328)

CR

8% (n=26/323) CABOMETYX + OPDIVO vs **4.6%** (n=15/328) sunitinib

PR

48% (n=154/323) CABOMETYX + OPDIVO vs **23%** (n=74/328) sunitinib

*PFS and ORR were assessed by BICR.[1]

IMPORTANT SAFETY INFORMATION (cont'd)
WARNINGS AND PRECAUTIONS

Diarrhea: Diarrhea occurred in 62% of CABOMETYX patients. Grade 3 diarrhea occurred in 10% of CABOMETYX patients. Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume at a reduced dose.

Palmar-Plantar Erythrodysesthesia (PPE): PPE occurred in 45% of CABOMETYX patients. Grade 3 PPE occurred in 13% of CABOMETYX patients. Withhold CABOMETYX until improvement to Grade 1 and resume at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

Hepatotoxicity: CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone.

Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes than when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST >3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

Adrenal Insufficiency: CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

Proteinuria: Proteinuria was observed in 8% of CABOMETYX patients. Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

Osteonecrosis of the Jaw (ONJ): ONJ occurred in <1% of CABOMETYX patients. ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain, or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to CABOMETYX initiation and periodically during treatment. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

Impaired Wound Healing: Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by characteristic findings on MRI, can occur with CABOMETYX. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

Thyroid Dysfunction: Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

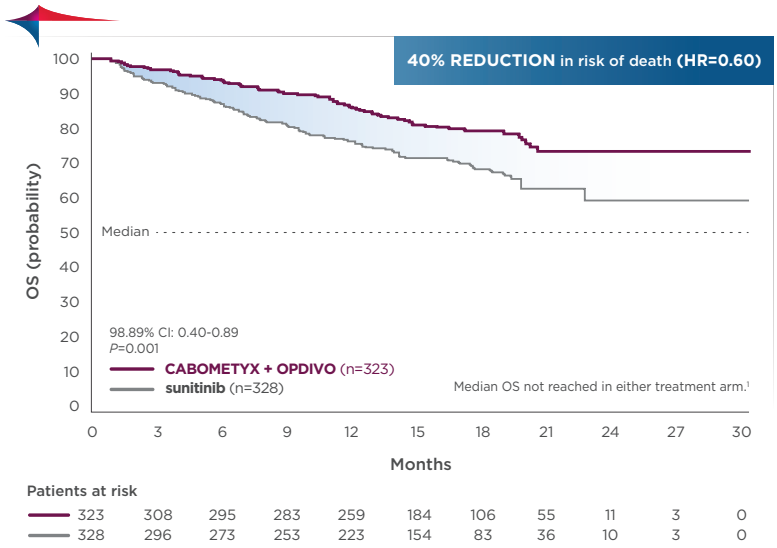
Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

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Early and sustained separation of OS curves in the primary analysis[1]

Secondary endpoint



CheckMate-9ER study design[1,2,5]

A randomized (1:1), open-label, Phase 3 trial vs sunitinib in 651 patients with previously untreated aRCC with a clear-cell component. The trial evaluated CABOMETYX 40 mg (starting dose) PO once daily in combination with OPDIVO 240 mg flat dose IV every 2 weeks vs sunitinib 50 mg (starting dose) PO once daily for 4 weeks, followed by 2 weeks off, per cycle. The primary endpoint was PFS, and secondary endpoints included OS, ORR, and safety. PFS and ORR were assessed by BICR. Quality of life was evaluated as an exploratory endpoint using the FKSI-19 scale, and the clinical significance is unknown. Other exploratory endpoints included biomarkers, PK, immunogenicity, and PFS-2. An updated efficacy analysis was conducted when 271 events were observed based on the pre-specified number of events for the pre-planned final analysis of OS.

Final analysis of OS (median follow-up: 32.9 months; range: 25.4-45.4 months): Median OS was 37.7 months for CABOMETYX + OPDIVO (95% CI: 35.5-NR; n=323) compared with 34.3 months for sunitinib (95% CI: 29.0-NR; n=328); HR=0.70 (95% CI: 0.55-0.90).[1,6-7]

Hypocalcemia: CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

Embryo-Fetal Toxicity: CABOMETYX can cause fetal harm. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX and advise them to use effective contraception during treatment and for 4 months after the last dose.

ADVERSE REACTIONS

The most common (≥20%) adverse reactions are:

CABOMETYX as a single agent: diarrhea, fatigue, PPE, decreased appetite, hypertension, nausea, vomiting, weight decreased, constipation.

CABOMETYX in combination with nivolumab: diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

DRUG INTERACTIONS

Strong CYP3A4 Inhibitors: If coadministration with strong CYP3A4 inhibitors cannot be avoided, reduce the CABOMETYX dosage. Avoid grapefruit or grapefruit juice.

Strong CYP3A4 Inducers: If coadministration with strong CYP3A4 inducers cannot be avoided, increase the CABOMETYX dosage. Avoid St. John's wort.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during CABOMETYX treatment and for 4 months after the final dose.

Hepatic Impairment: In patients with moderate hepatic impairment, reduce the CABOMETYX dosage. Avoid CABOMETYX in patients with severe hepatic impairment.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

For additional safety information, please see Brief Summary of the Prescribing Information for CABOMETYX on following pages.

BICR=blinded independent central review; CR=complete response; ITT=intent to treat; IV=intravenous; PFS-2=progression-free survival after subsequent therapy; PK=pharmacokinetics; PO=by mouth; PR=partial response.

References: 1. CABOMETYX® (cabozantinib) Prescribing Information. Exelixis Inc; 2022. **2.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med*. 2021;384(9):829-841. **3.** Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma: first results from the randomized phase 3 CheckMate 9ER trial. Presented at The European Society for Medical Oncology (ESMO) Virtual Congress 2020; September 19-21, 2020. Presentation 6960. **4.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [supplementary appendix]. *N Engl J Med*. 2021;384(9):829-841. **5.** Choueiri TK, Powles T, Burotto M, et al; CheckMate 9ER Investigators. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma [protocol]. *N Engl J Med*. 2021;384(9):829-841. **6.** Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. *Lancet Oncol*. 2022;23(7):888-898. **7.** Data on file. Exelixis, Inc.

CABOMETYX® (cabozantinib) tablets + OPDIVO® (nivolumab)

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BRIEF SUMMARY OF PRESCRIBING INFORMATION.

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INITIAL U.S. APPROVAL: 2012

1 INDICATIONS AND USAGE

1.1 Renal Cell Carcinoma
CABOMETYX is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of patients with advanced RCC.

1.2 Hepatocellular Carcinoma
CABOMETYX is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

1.3 Differentiated Thyroid Cancer
CABOMETYX is indicated for the treatment of adult and pediatric patients 12 years of age and older with locally advanced or metastatic differentiated thyroid cancer (DTC) that has progressed following prior VEGFR-targeted therapy and who are radioactive iodine-refractory or ineligible.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage
Severe and fatal hemorrhages occurred with CABOMETYX. The incidence of Grade 3 to 5 hemorrhagic events was 5% in CABOMETYX patients in the RCC, HCC, and DTC studies.

Discontinue CABOMETYX for Grade 3 or 4 hemorrhage and prior to surgery as recommended. Do not administer CABOMETYX to patients who have a recent history of hemorrhage, including hemoptysis, hematemesis, or melena.

5.2 Perforations and Fistulas
Fistulas, including fatal cases, occurred in 1% of CABOMETYX-treated patients. Gastrointestinal (GI) perforations, including fatal cases, occurred in 1% of CABOMETYX-treated patients.

Monitor patients for signs and symptoms of fistulas and perforations, including abscess and sepsis. Discontinue CABOMETYX in patients who experience a Grade 4 fistula or a GI perforation.

5.3 Thrombotic Events
CABOMETYX increased the risk of thrombotic events. Venous thromboembolism occurred in 7% (including 4% pulmonary embolism) and arterial thromboembolism occurred in 2% of CABOMETYX-treated patients. Fatal thrombotic events occurred in CABOMETYX-treated patients.

Discontinue CABOMETYX in patients who develop an acute myocardial infarction or serious arterial or venous thromboembolic events that require medical intervention.

5.4 Hypertension and Hypertensive Crisis
CABOMETYX can cause hypertension, including hypertensive crisis. Hypertension was reported in 37% (16% Grade 3 and <1% Grade 4) of CABOMETYX-treated patients.

Do not initiate CABOMETYX in patients with uncontrolled hypertension. Monitor blood pressure regularly during CABOMETYX treatment. Withhold CABOMETYX for hypertension that is not adequately controlled with medical management; when controlled, resume CABOMETYX at a reduced dose. Permanently discontinue CABOMETYX for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

5.5 Diarrhea
Diarrhea occurred in 62% of patients treated with CABOMETYX. Grade 3 diarrhea occurred in 10% of patients treated with CABOMETYX.

Monitor and manage patients using antidiarrheals as indicated. Withhold CABOMETYX until improvement to ≤ Grade 1, resume CABOMETYX at a reduced dose.

5.6 Palmar-Plantar Erythrodysesthesia
Palmar-plantar erythrodysesthesia (PPE) occurred in 45% of patients treated with CABOMETYX. Grade 3 PPE occurred in 13% of patients treated with CABOMETYX.

Withhold CABOMETYX until improvement to Grade 1 and resume CABOMETYX at a reduced dose for intolerable Grade 2 PPE or Grade 3 PPE.

5.7 Hepatotoxicity
CABOMETYX in combination with nivolumab can cause hepatic toxicity with higher frequencies of Grades 3 and 4 ALT and AST elevations compared to CABOMETYX alone. Monitor liver enzymes before initiation of and periodically throughout treatment. Consider more frequent monitoring of liver enzymes as compared to when the drugs are administered as single agents. For elevated liver enzymes, interrupt CABOMETYX and nivolumab and consider administering corticosteroids.

With the combination of CABOMETYX and nivolumab, Grades 3 and 4 increased ALT or AST were seen in 11% of patients. ALT or AST > 3 times ULN (Grade ≥2) was reported in 83 patients, of whom 23 (28%) received systemic corticosteroids; ALT or AST resolved to Grades 0-1 in 74 (89%). Among the 44 patients with Grade ≥2 increased ALT or AST who were rechallenged with either CABOMETYX (n=9) or nivolumab (n=11) as a single agent or with both (n=24), recurrence of Grade ≥2 increased ALT or AST was observed in 2 patients receiving CABOMETYX, 2 patients receiving nivolumab, and 7 patients receiving both CABOMETYX and nivolumab. Withhold and resume at a reduced dose based on severity.

5.8 Adrenal Insufficiency
CABOMETYX in combination with nivolumab can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold CABOMETYX and/or nivolumab and resume CABOMETYX at a reduced dose depending on severity.

Adrenal insufficiency occurred in 4.7% (15/320) of patients with RCC who received CABOMETYX with nivolumab, including Grade 3 (2.2%), and Grade 2 (1.9%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of CABOMETYX and nivolumab in 0.9% and withholding of CABOMETYX and nivolumab in 2.8% of patients with RCC.

Approximately 80% (12/15) of patients with adrenal insufficiency received hormone replacement therapy, including systemic corticosteroids. Adrenal insufficiency resolved in 27% (n=4) of the 15 patients. Of the 9 patients in whom CABOMETYX with nivolumab was withheld for adrenal insufficiency, 6 reinstated treatment after symptom improvement; of these, all (n=6) received hormone replacement therapy and 2 had recurrence of adrenal insufficiency.

5.9 Proteinuria
Proteinuria was observed in 8% of patients receiving CABOMETYX.

Monitor urine protein regularly during CABOMETYX treatment. For Grade 2 or 3 proteinuria, withhold CABOMETYX until improvement to ≤ Grade 1 proteinuria, resume CABOMETYX at a reduced dose. Discontinue CABOMETYX in patients who develop nephrotic syndrome.

5.10 Osteonecrosis of the Jaw
Osteonecrosis of the jaw (ONJ) occurred in <1% of patients treated with CABOMETYX.

ONJ can manifest as jaw pain, osteomyelitis, osteitis, bone erosion, tooth or periodontal infection, toothache, gingival ulceration or erosion, persistent jaw pain or slow healing of the mouth or jaw after dental surgery. Perform an oral examination prior to initiation of CABOMETYX and periodically during CABOMETYX. Advise patients regarding good oral hygiene practices. Withhold CABOMETYX for at least 3 weeks prior to scheduled dental surgery or invasive dental procedures, if possible. Withhold CABOMETYX for development of ONJ until complete resolution, resume at a reduced dose.

5.11 Impaired Wound Healing
Wound complications occurred with CABOMETYX. Withhold CABOMETYX for at least 3 weeks prior to elective surgery. Do not administer CABOMETYX for at least 2 weeks after major surgery and until adequate wound healing. The safety of resumption of CABOMETYX after resolution of wound healing complications has not been established.

5.12 Reversible Posterior Leukoencephalopathy Syndrome
Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by characteristic finding on MRI, can occur with CABOMETYX. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. Discontinue CABOMETYX in patients who develop RPLS.

5.13 Thyroid Dysfunction
Thyroid dysfunction, primarily hypothyroidism, has been observed with CABOMETYX. Based on the safety population, thyroid dysfunction occurred in 19% of patients treated with CABOMETYX, including Grade 3 in 0.4% of patients.

Patients should be assessed for signs of thyroid dysfunction prior to the initiation of CABOMETYX and monitored for signs and symptoms of thyroid dysfunction during CABOMETYX treatment. Thyroid function testing and management of dysfunction should be performed as clinically indicated.

5.14 Hypocalcemia
CABOMETYX can cause hypocalcemia. Based on the safety population, hypocalcemia occurred in 13% of patients treated with CABOMETYX, including Grade 3 in 2% and Grade 4 in 1% of patients. Laboratory abnormality data were not collected in CABOSUN.

In COSMIC-311, hypocalcemia occurred in 36% of patients treated with CABOMETYX, including Grade 3 in 6% and Grade 4 in 3% of patients.

Monitor blood calcium levels and replace calcium as necessary during treatment. Withhold and resume at reduced dose upon recovery or permanently discontinue CABOMETYX depending on severity.

5.15 Embryo-Fetal Toxicity
Based on data from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. Cabozantinib administration to pregnant animals during organogenesis resulted in embryolethality at exposures below those occurring clinically at the recommended dose, and in increased incidences of skeletal variations in rats and visceral variations and malformations in rabbits.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the last dose.

6 ADVERSE REACTIONS
The following clinically significant adverse reactions are discussed elsewhere in the labeling: Hemorrhage, Perforations and Fistulas, Thrombotic Events, Hypertension and Hypertensive Crisis, Diarrhea, Palmar-plantar Erythrodysesthesia, Hepatotoxicity, Adrenal Insufficiency, Proteinuria, Osteonecrosis of the Jaw, Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome, Thyroid Dysfunction and Hypocalcemia.

6.1 Clinical Trial Experience
The data described in the WARNINGS AND PRECAUTIONS section and below reflect exposure to CABOMETYX as a single agent in 409 patients with RCC enrolled in randomized, active-controlled trials (CABOSUN, METEOR), 467 patients with HCC enrolled in a randomized, placebo-controlled trial (CELESTIAL), in 125 patients with DTC enrolled in a randomized, placebo-controlled trial (COSMIC-311), and in combination with nivolumab 240 mg/m^2 every 2 weeks in 320 patients with RCC enrolled in a randomized, active-controlled trial (CHECKMATE-9ER).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Renal Cell Carcinoma

METEOR

The safety of CABOMETYX was evaluated in METEOR, a randomized, open-label trial in which 331 patients with advanced renal cell carcinoma received CABOMETYX 60 mg once daily and 322 patients received everolimus 10 mg once daily until disease progression or unacceptable toxicity. Patients on both arms who had disease progression could continue treatment at the discretion of the investigator. The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving CABOMETYX and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

Adverse reactions which occurred in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency, were: diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia (PPE), hypertension, vomiting, weight decreased, and constipation. Grade 3-4 adverse reactions and laboratory abnormalities which occurred in ≥ 5% of patients were hypertension, diarrhea, fatigue, PPE, hyponatremia, hypophosphatemia, hypomagnesemia, lymphopenia, anemia, hypokalemia, and increased GGT.

The dose was reduced in 60% of patients receiving CABOMETYX and in 24% of patients receiving everolimus. Twenty percent (20%) of patients received CABOMETYX 20 mg once daily as their lowest dose. The most frequent adverse reactions leading to dose reduction in patients treated with CABOMETYX were: diarrhea, PPE, fatigue, and hypertension. Adverse reactions leading to dose interruption occurred in 70% patients receiving CABOMETYX and in 59% patients receiving everolimus. Adverse reactions led to study treatment discontinuation in 10% of patients receiving CABOMETYX and in 10% of patients receiving everolimus. The most frequent adverse reactions leading to permanent discontinuation in patients treated with CABOMETYX were decreased appetite (2%) and fatigue (1%).

Table 1. Adverse Reactions Occurring in ≥ 10% Patients Who Received CABOMETYX in METEOR

Adverse Reaction	CABOMETYX (n=331)[1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	74	11	28	2
Nausea	50	4	28	<1
Vomiting	32	2	14	<1
Stomatitis	22	2	24	2
Constipation	25	<1	19	<1
Abdominal pain[3]	23	4	13	2
Dyspepsia	12	<1	5	0
General				
Fatigue	56	9	47	7
Mucosal inflammation	19	<1	23	3
Asthenia	19	4	16	2

Adverse Reaction	CABOMETYX (n=331)[1]		Everolimus (n=322)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Metabolism and Nutrition				
Decreased appetite	46	3	34	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	42	8	6	<1
Rash[4]	23	<1	43	<1
Dry skin	11	0	10	0
Vascular				
Hypertension[5]	39	16	8	3
Investigations				
Weight decreased	31	2	12	0
Nervous System				
Dysgeusia	24	0	9	0
Headache	11	<1	12	<1
Dizziness	11	0	7	0
Endocrine				
Hypothyroidism	21	0	<1	<1
Respiratory, Thoracic, and Mediastinal				
Dysphonia	20	<1	4	0
Dyspnea	19	3	29	4
Cough	18	<1	33	<1
Blood and Lymphatic				
Anemia	17	5	38	16
Musculoskeletal and Connective Tissue				
Pain in extremity	14	1	8	<1
Muscle spasms	13	0	5	0
Arthralgia	11	<1	14	1
Renal and Urinary				
Proteinuria	12	2	9	<1

[1] One subject randomized to everolimus received cabozantinib.
[2] National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
[3] Includes the following terms: abdominal pain, abdominal pain upper, and abdominal pain lower
[4] Includes the following terms: rash, rash erythematous, rash follicular, rash macular, rash papular, rash pustular, rash vesicular, genital rash, intermittent leg rash, rash on scrotum and penis, rash maculo-papular, rash pruritic, contact dermatitis, dermatitis acneiform
[5] Includes the following terms hypertension, blood pressure increased, hypertensive crisis, blood pressure fluctuation

Other clinically important adverse reactions (all grades) that were reported in <10% of patients treated with CABOMETYX included: wound complications (2%), convulsion (<1%), pancreatitis (<1%), osteonecrosis of the jaw (<1%), and hepatitis cholestatic (<1%).

Table 2. Laboratory Abnormalities Occurring in ≥ 25% Patients Who Received CABOMETYX in METEOR

Laboratory Abnormality	CABOMETYX (n=331)		Everolimus (n=322)	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage (%) of Patients			
Chemistry				
Increased AST	74	3	40	<1
Increased ALT	68	3	32	<1
Increased creatinine	58	<1	71	0
Increased triglycerides	53	4	73	13
Hypophosphatemia	48	8	36	5
Hyperglycemia	37	2	59	8
Hypoalbuminemia	36	2	28	<1
Increased ALP	35	2	29	1
Hypomagnesemia	31	7	4	<1
Hyponatremia	30	8	26	6
Increased GGT	27	5	43	9
Hematology				
Leukopenia	35	<1	31	<1
Neutropenia	31	2	17	<1
Anemia[1]	31	4	71	17
Lymphopenia	25	7	39	12
Thrombocytopenia	25	<1	27	<1

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase.
NCI CTCAE, Version 4.0
[1] Based on laboratory abnormalities

CABOSUN

The safety of CABOMETYX was evaluated in CABOSUN, a randomized, open-label trial in patients with advanced renal cell carcinoma, in which 78 patients received CABOMETYX 60 mg once daily and 72 patients received sunitinib 50 mg once daily (4 weeks on treatment followed by 2 weeks off), until disease progression or unacceptable toxicity. The median duration of treatment was 6.5 months (range 0.2 – 28.7) for patients receiving CABOMETYX and 3.1 months (range 0.2 – 25.5) for patients receiving sunitinib.

Within 30 days of treatment, there were 4 deaths in patients treated with CABOMETYX and 6 deaths in patients treated with sunitinib. Of the 4 patients treated with CABOMETYX, 2 patients died due to gastrointestinal perforation, 1 patient had acute renal failure, and 1 patient died due to clinical deterioration. All Grade 3-4 adverse reactions were collected in the entire safety population. The most frequent Grade 3-4 adverse reactions (≥5%) in patients treated with CABOMETYX were hypertension, diarrhea, hyponatremia, hypophosphatemia, PPE, fatigue, increased ALT, decreased appetite, stomatitis, pain, hypotension, and syncope.

The median average daily dose was 50.3 mg for CABOMETYX and 44.7 mg for sunitinib (excluding scheduled sunitinib non-dosing days). The dose was reduced in 46% of patients receiving CABOMETYX and in 35% of patients receiving sunitinib. The dose was held in 73% of patients receiving CABOMETYX and in 71% of patients receiving sunitinib. Based on patient disposition, 21% of patients receiving CABOMETYX and 22% of patients receiving sunitinib discontinued due to an adverse reaction.

Table 3. Grade 3-4 Adverse Reactions Occurring in ≥ 1% Patients Who Received CABOMETYX in CABOSUN

Adverse Reaction	CABOMETYX (n = 78)	Sunitinib (n = 72)
	Grade 3-4[1]	Grade 3-4[1]
	Percentage (%) of Patients	
Patients with any Grade 3-4 Adverse Reaction	68	65
Gastrointestinal		
Diarrhea	10	11
Stomatitis	5	6
Nausea	3	4
Vomiting	1	3
Constipation	1	0
General		
Fatigue	6	17
Pain	5	0
Metabolism and Nutrition		
Hyponatremia[2]	9	8
Hypophosphatemia[2]	9	7
Decreased appetite	5	1
Dehydration	4	1
Hypocalcemia[2]	3	0
Hypomagnesemia[2]	3	0
Hyperkalemia[2]	1	3
Skin and Subcutaneous Tissue		
Palmar-plantar erythrodysesthesia	8	4
Skin ulcer	3	0
Vascular		
Hypertension[3]	28	21
Hypotension	5	1
Angiopathy	1	1
Investigations		
Increased ALT[2]	5	0
Weight decreased	4	0
Increased AST[2]	3	3
Increased blood creatinine[2]	3	3
Lymphopenia[2]	1	6
Thrombocytopenia[2]	1	11
Nervous System		
Syncope	5	0
Respiratory, Thoracic, and Mediastinal		
Dyspnea	1	6
Dysphonia	1	0
Blood and Lymphatic		
Anemia	1	3
Psychiatric		
Depression	4	0
Confusional state	1	1
Infections		
Lung infection	4	0
Musculoskeletal and Connective Tissue		
Back pain	4	0
Bone pain	3	1
Pain in extremity	3	0
Arthralgia	1	0
Renal and Urinary		
Renal failure acute	4	1
Proteinuria	3	1

ALT, alanine aminotransferase; AST, aspartate aminotransferase
[1] NCI CTCAE Version 4.0
[2] Laboratory abnormalities are reported as adverse reactions and not based on shifts in laboratory values
[3] Includes the following term: hypertension

CHECKMATE-9ER

The safety of CABOMETYX with nivolumab was evaluated in CHECKMATE-9ER, a randomized, open-label study in patients with previously untreated advanced RCC. Patients received CABOMETYX 40 mg orally once daily with nivolumab 240 mg over 30 minutes every 2 weeks (n=320) or sunitinib 50 mg daily, administered orally for 4 weeks on treatment followed by 2 weeks off (n=320). CABOMETYX could be interrupted or reduced to 20 mg daily or 20 mg every other day. The median duration of treatment was 14 months (range: 0.2 to 27 months) in CABOMETYX and nivolumab-treated patients. In this trial, 82% of patients in the CABOMETYX and nivolumab arm were exposed to treatment for >6 months and 60% of patients were exposed to treatment for >1 year.

Serious adverse reactions occurred in 48% of patients receiving CABOMETYX and nivolumab.

The most frequent (≥2%) serious adverse reactions were diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia. Fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either CABOMETYX or nivolumab occurred in 20% of patients: 8% CABOMETYX only, 7% nivolumab only, and 6% both drugs due to the same adverse reaction at the same time. Adverse reactions leading to dose interruption or reduction of either CABOMETYX or nivolumab occurred in 83% of patients: 46% CABOMETYX only, 3% nivolumab only, and 21% both drugs due to the same adverse reaction at the same time, and 6% both drugs sequentially.

The most common adverse reactions reported in ≥20% of patients treated with CABOMETYX and nivolumab were diarrhea, fatigue, hepatotoxicity, PPE, stomatitis, rash, hypertension, hypothyroidism, musculoskeletal pain, decreased appetite, nausea, dysgeusia, abdominal pain, cough, and upper respiratory tract infection.

Table 4. Adverse Reactions in ≥15% of Patients receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

Adverse Reaction	CABOMETYX and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	64	7	47	4.4
Nausea	27	0.6	31	0.3
Abdominal Pain[a]	22	1.9	15	0.3
Vomiting	17	1.9	21	0.3
Dyspepsia[b]	15	0	22	0.3
General				
Fatigue[c]	51	8	50	8
Hepatobiliary				
Hepatotoxicity[d]	44	11	26	5
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	40	8	41	8
Stomatitis[e]	37	3.4	46	4.4
Rash[f]	36	3.1	14	0
Pruritus	19	0.3	4.4	0
Vascular				
Hypertension[g]	36	13	39	14
Endocrine				
Hypothyroidism[h]	34	0.3	30	0.3
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[i]	33	3.8	29	3.1
Arthralgia	18	0.3	9	0.3
Metabolism and Nutrition				
Decreased appetite	28	1.9	20	1.3
Nervous System Disorders				
Dysgeusia	24	0	22	0
Headache	16	0	12	0.6
Respiratory, Thoracic, and Mediastinal				
Cough[j]	20	0.3	17	0
Dysphonia	17	0.3	3.4	0

Adverse Reaction	CABOMETYX and Nivolumab (n=320)		Sunitinib (n=320)	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 3-4
	Percentage (%) of Patients			
Infections and Infestations				
Upper respiratory tract infection[k]	20	0.3	8	0.3

Toxicity was graded per NCI CTCAE v4.

[a] Includes abdominal discomfort, abdominal pain lower, abdominal pain upper.

[b] Includes gastroesophageal reflux disease.

[c] Includes asthenia.

[d] Includes hepatotoxicity, ALT increased, AST increased, blood alkaline phosphatase increased, gamma-glutamyl transferase increased, autoimmune hepatitis, blood bilirubin increased, drug induced liver injury, hepatic enzyme increased, hepatitis, hyperbilirubinemia, liver function test increased, liver function test abnormal, transaminases increased, hepatic failure.

[e] Includes mucosal inflammation, aphthous ulcer, mouth ulceration.

[f] Includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic.

[g] Includes blood pressure increased, blood pressure systolic increased.

[h] Includes primary hypothyroidism.

[i] Includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain.

[j] Includes productive cough.

[k] Includes nasopharyngitis, pharyngitis, rhinitis

Table 5. Laboratory Values Worsening from Baseline[a] Occurring in >20% of Patients receiving CABOMETYX and Nivolumab-CHECKMATE-9ER

Laboratory Abnormality	CABOMETYX and Nivolumab		Sunitinib	
	Grades 1-4	Grades 3-4	Grades 1-4	Grades 1-4
	Percentage (%) of Patients			
Chemistry				
Increased ALT	79	9.8	39	3.5
Increased AST	77	7.9	57	2.6
Hypophosphatemia	69	28	48	10
Hypocalcemia	54	1.9	24	0.6
Hypomagnesemia	47	1.3	25	0.3
Hyperglycemia	44	3.5	44	1.7
Hyponatremia	43	11	36	12
Increased lipase	41	14	38	13
Increased amylase	41	10	28	6
Increased alkaline phosphatase	41	2.8	37	1.6
Increased creatinine	39	1.3	42	0.6
Hyperkalemia	35	4.7	27	1
Hypoglycemia	26	0.8	14	0.4
Hematology				
Lymphopenia	42	6.6	45	10
Thrombocytopenia	41	0.3	70	9.7
Anemia	37	2.5	61	4.8
Leukopenia	37	0.3	66	5.1
Neutropenia	35	3.2	67	12

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: CABOMETYX and nivolumab group (range: 170 to 317 patients) and sunitinib group (range: 173 to 311 patients).

Hepatocellular Carcinoma

The safety of CABOMETYX was evaluated in CELESTIAL, a randomized, double-blind, placebo-controlled trial in which 704 patients with advanced hepatocellular carcinoma were randomized to receive CABOMETYX 60 mg orally once daily (n=467) or placebo (n=237) until disease progression or unacceptable toxicity. The median duration of treatment was 3.8 months (range 0.1 – 37.3) for patients receiving CABOMETYX and 2.0 months (range 0.0 – 27.2) for patients receiving placebo. The population exposed to CABOMETYX was 81% male, 56% White, and had a median age of 64 years.

Adverse reactions occurring in ≥ 25% of CABOMETYX- treated patients, in order of decreasing frequency were: diarrhea, decreased appetite, PPE, fatigue, nausea, hypertension, and vomiting. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, asthenia, and decreased appetite. There were 6 adverse reactions leading to death in patients receiving CABOMETYX (hepatic failure, hepatorenal syndrome, esophagobronchial fistula, portal vein thrombosis, pulmonary embolism, upper gastrointestinal hemorrhage).

The median average daily dose was 35.8 mg for CABOMETYX. The dose was reduced in 62% of patients receiving CABOMETYX; 33% of patients required a reduction to 20 mg daily. The most frequent adverse reactions or laboratory abnormalities leading to dose reduction of CABOMETYX were: PPE, diarrhea, fatigue, hypertension, and increased AST. Adverse reactions leading to dose interruption occurred in 84% patients receiving CABOMETYX. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 16% of patients. The most frequent adverse reactions leading to permanent discontinuation of CABOMETYX were PPE (2%), fatigue (2%), decreased appetite (1%), diarrhea (1%), and nausea (1%).

Table 6. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Adverse Reaction	CABOMETYX (n = 467)		Placebo (n = 237)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	54	10	19	2
Nausea	31	2	18	2
Vomiting	26	<1	12	3
Stomatitis	13	2	2	0
Dyspepsia	10	0	3	0
General				
Fatigue	45	10	30	4
Asthenia	22	7	8	2
Mucosal inflammation	14	2	2	<1
Metabolism and Nutrition				
Decreased appetite	48	6	18	<1
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	17	5	0
Rash[3]	21	2	9	<1
Vascular				
Hypertension[4]	30	16	6	2
Investigations				
Weight decreased	17	1	6	0
Nervous System				
Dysgeusia	12	0	2	0
Endocrine				
Hypothyroidism	8	<1	<1	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	19	1	2	0
Dyspnea	12	3	10	<1
Musculoskeletal and Connective Tissue				
Pain in extremity	9	<1	4	1
Muscle spasms	8	<1	2	0

[1] Includes terms with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] NCI CTCAE Version 4.0

[3] Includes the following terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, dermatitis, dermatitis acneiform, dermatitis contact, dermatitis diaper, dermatitis exfoliative, dermatitis infected

[4] Includes the following terms: hypertension, blood pressure diastolic increased, blood pressure increased

Table 7. Laboratory Abnormalities Occurring in ≥5% of CABOMETYX-Treated Patients in CELESTIAL[1]

Laboratory Abnormality	CABOMETYX N=467		Placebo N=237	
	All Grades	Grade 3-4	All Grades	Grade 3-4
	Percentage of Patients			
Chemistry				
Increased LDH	84	9	29	2
Increased ALT	73	12	37	6
Increased AST	73	24	46	19
Hypoalbuminemia	51	1	32	1
Increased ALP	43	8	38	6
Hypophosphatemia	25	9	8	4
Hypokalemia	23	6	6	1
Hypomagnesemia	22	3	3	0
Increased amylase	16	2	9	2
Hypocalcemia	8	2	0	0
Hematology				
Decreased platelets	54	10	16	1
Neutropenia	43	7	8	1
Increased hemoglobin	8	0	1	0

[1] Includes laboratory abnormalities with a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, blood lactate dehydrogenase

Differentiated Thyroid Cancer

The safety of CABOMETYX was evaluated in COSMIC-311, a randomized, double-blind, placebo-controlled trial in which 187 patients with advanced differentiated thyroid cancer were randomized to receive CABOMETYX 60 mg orally once daily (n=125) or placebo (n=62) with supportive care until disease progression or unacceptable toxicity. At the time of the primary efficacy analysis, the median duration of treatment was 4.4 months (range 0.0 – 15.7) for patients receiving CABOMETYX and 2.3 months (range 0.3 – 11.6) for patients receiving placebo. The median age was 66 years (range 32 to 85 years), 55% were female, 70% were White, 18% were Asian, 2% were Black, 2% were American Indian or Alaska Native, and 63% received prior lenvatinib.

Adverse reactions occurring in ≥ 25% of CABOMETYX-treated patients, in order of decreasing frequency were: diarrhea, PPE, fatigue, hypertension, and stomatitis. Grade 3-4 adverse reactions which occurred in ≥ 5% of patients were PPE, hypertension, fatigue, diarrhea, and stomatitis. Serious adverse reactions occurred in 34% of patients who received CABOMETYX. Serious adverse reactions in ≥2% included diarrhea, pleural effusion, pulmonary embolism and dyspnea. Fatal adverse reactions occurred in 1.6% of patients in the CABOMETYX arm, including arterial hemorrhage (0.8%) and pulmonary embolism (0.8%).

The median average daily dose was 42.0 mg for CABOMETYX. The dose was reduced in 56% of patients receiving CABOMETYX; 22% of patients required a second dose reduction. The most frequent adverse reactions (≥5%) leading to dose reduction of CABOMETYX were PPE, diarrhea, fatigue, proteinuria, and decreased appetite. Dose interruptions occurred in 72% patients receiving CABOMETYX. Adverse reactions requiring dosage interruption in ≥5% of patients were PPE, diarrhea, dyspnea, hypertension, decreased appetite and proteinuria. Adverse reactions leading to permanent discontinuation of CABOMETYX occurred in 5% of patients.

Table 8. Adverse Reactions Occurring in ≥5% of CABOMETYX-Treated Patients in COSMIC-311[1]

Adverse Reaction	CABOMETYX (N=125)		Placebo (N=62)	
	All Grades[2]	Grade 3-4	All Grades[2]	Grade 3-4
	Percentage (%) of Patients			
Gastrointestinal				
Diarrhea	51	7	3	0
Nausea	24	3	2	0
Vomiting	14	1	8	0
Stomatitis[3]	26	5	3	0
Dry mouth	10	1	2	0
General				
Fatigue[4]	42	10	23	0
Metabolism and Nutrition				
Decreased appetite	23	3	16	0
Skin and Subcutaneous Tissue				
Palmar-plantar erythrodysesthesia	46	10	0	0
Vascular				
Hypertension[5]	30	10	5	3
Investigations				
Weight decreased	18	1	5	0
Nervous System				
Dysgeusia	10	0	0	0
Headache	10	2	2	0
Respiratory, Thoracic, and Mediastinal				
Dysphonia	10	0	2	0
Pulmonary embolism	5	2	0	0
Renal and Urinary				
Proteinuria	15	1	3	0

[1] Includes terms that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] NCI CTCAE Version 5.0

[3] Includes the following terms: mucosal inflammation, stomatitis

[4] Includes the following terms: fatigue, asthenia

[5] Includes the following terms: hypertension, blood pressure increased, hypertensive crisis

Table 9. Laboratory Abnormalities Occurring in ≥10% of CABOMETYX-Treated Patients in COSMIC-311[1]

Laboratory Abnormality	CABOMETYX N=125		Placebo N=62	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
	Percentage (%) of Patients			
Chemistry				
LDH increased[2]	90	10	32	3
AST increased	77	1	18	0
ALT increased	66	2	11	0
Hypocalcemia	36	9	10	2
ALP increased	34	0	15	0
GGT increased	26	2	21	2
Hypomagnesemia	25	2	5	0
Hypoalbuminemia	19	1	7	0
Hypokalemia	18	1	3	0
Hyponatremia	15	0	10	2
Hyperbilirubinemia	12	0	5	0
Hematology				
Leukocytes decreased	38	2	7	2
Neutrophils decreased	31	2	5	2
Platelets decreased	26	0	5	0

[1] Includes laboratory abnormalities that are more frequent in the CABOMETYX arm and have a between-arm difference of ≥ 5% (all grades) or ≥ 2% (Grade 3-4)

[2] Sponsor-defined grades for LDH were as follows: Grade 1 (> ULN to ≤ 2 × ULN), Grade 2 (> 2 × ULN to ≤ 3 × ULN), Grade 3 (> 3 × ULN).

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; LDH, blood lactate dehydrogenase

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on CABOMETYX

Strong CYP3A4 Inhibitors

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inhibitor increased the exposure of cabozantinib, which may increase the risk of exposure-related adverse reactions. Avoid coadministration of CABOMETYX with strong CYP3A4 inhibitors. Reduce the dosage of CABOMETYX if coadministration with strong CYP3A4 inhibitors cannot be avoided. Avoid grapefruit or grapefruit juice which may also increase exposure of cabozantinib.

Strong CYP3A Inducers

Coadministration of a cabozantinib capsule formulation with a strong CYP3A4 inducer decreased the exposure of cabozantinib, which may reduce efficacy. Avoid coadministration of CABOMETYX with strong CYP3A4 inducers. Increase the dosage of CABOMETYX if coadministration with strong CYP3A4 inducers cannot be avoided. Avoid St. John's wort which may also decrease exposure of cabozantinib.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and its mechanism of action, CABOMETYX can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. In animal developmental and reproductive toxicology studies administration of cabozantinib to pregnant rats and rabbits during organogenesis resulted in embryofetal lethality and structural anomalies at exposures that were below those occurring clinically at the recommended dose (see Data). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In an embryo-fetal development study in pregnant rats, daily oral administration of cabozantinib throughout organogenesis caused increased embryo-fetal lethality compared to controls at a dose of 0.03 mg/kg (approximately 0.12-fold of human area under the curve [AUC] at the recommended dose). Findings included delayed ossification and skeletal variations at a dose of 0.01 mg/kg/day (approximately 0.04-fold of human AUC at the recommended dose).

In pregnant rabbits, daily oral administration of cabozantinib throughout organogenesis resulted in findings of visceral malformations and variations including reduced spleen size and missing lung lobe at 3 mg/kg (approximately 1.1-fold of the human AUC at the recommended dose).

In a pre- and postnatal study in rats, cabozantinib was administered orally from gestation day 10 through postnatal day 20. Cabozantinib did not produce adverse maternal toxicity or affect pregnancy, parturition or lactation of female rats, and did not affect the survival, growth or postnatal development of the offspring at doses up to 0.3 mg/kg/day (0.05-fold of the maximum recommended clinical dose).

8.2 Lactation

Risk Summary

There is no information regarding the presence of cabozantinib or its metabolites in human milk, or their effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in breastfed children, advise women not to breastfeed during treatment with CABOMETYX and for 4 months after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating CABOMETYX.

Contraception

CABOMETYX can cause fetal harm when administered to a pregnant woman.

Females

Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Infertility

Females and Males

Based on findings in animals, CABOMETYX may impair fertility in females and males of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of CABOMETYX for the treatment of differentiated thyroid cancer (DTC) have been established in pediatric patients aged 12 years and older.

Use of CABOMETYX in pediatric patients aged 12 years and older with DTC is supported by evidence from adequate and well-controlled studies of CABOMETYX in adults with additional population pharmacokinetic data demonstrating that cabozantinib exposure is within the same range between adults and pediatric patients aged 12 years and older at the recommended dosages.

The safety and effectiveness of CABOMETYX in pediatric patients less than 12 years of age have not been established.

Juvenile Animal Toxicity Data

Juvenile rats were administered cabozantinib at doses of 1 or 2 mg/kg/day from Postnatal Day 12 (comparable to less than 2 years in humans) through Postnatal Day 35 or 70. Mortalities occurred at doses ≥1 mg/kg/day (approximately 0.16 times the clinical dose of 60 mg/day based on body surface area). Hypoactivity was observed at both doses tested on Postnatal Day 22. Targets were generally similar to those seen in adult animals, occurred at both doses, and included the kidney (nephropathy, glomerulonephritis), reproductive organs, gastrointestinal tract (cystic dilatation and hyperplasia in Brunner's gland and inflammation of duodenum; and epithelial hyperplasia of colon and cecum), bone marrow (hypocellularity and lymphoid depletion), and liver. Tooth abnormalities and whitening as well as effects on bones including reduced bone mineral content and density, physeal hypertrophy, and decreased cortical bone also occurred at all dose levels. Recovery was not assessed at a dose of 2 mg/kg (approximately 0.32 times the clinical dose of 60 mg based on body surface area) due to high levels of mortality. At the low dose level, effects on bone parameters were partially resolved but effects on the kidney and epididymis/testis persisted after treatment ceased.

8.5 Geriatric Use

In CABOSUN and METEOR, 41% of 409 patients treated with CABOMETYX were age 65 years and older, and 8% were 75 years and older. In CELESTIAL, 49% of 467 patients treated with CABOMETYX were age 65 years and older, and 15% were 75 years and older. In COSMIC-311, 50% of 125 patients treated with CABOMETYX were age 65 years and older, and 12% were 75 years and older.

No overall differences in safety or effectiveness were observed between these patients and younger patients.

Of the 320 patients randomized to CABOMETYX administered with nivolumab in CHECKMATE-9ER, 41% were 65 years or older and 9% were 75 years or older. No overall difference in safety was reported between elderly patients and younger patients.

8.6 Hepatic Impairment

Increased exposure to cabozantinib has been observed in patients with moderate (Child-Pugh B) hepatic impairment. Reduce the CABOMETYX dose in patients with moderate hepatic impairment. Avoid CABOMETYX in patients with severe hepatic impairment (Child-Pugh C), since it has not been studied in this population.

8.7 Renal Impairment

No dosage adjustment is recommended in patients with mild or moderate renal impairment. There is no experience with CABOMETYX in patients with severe renal impairment.

10 OVERDOSAGE

One case of overdosage was reported following administration of another formulation of cabozantinib; a patient inadvertently took twice the intended dose for 9 days. The patient suffered Grade 3 memory impairment, Grade 3 mental status changes, Grade 3 cognitive disturbance, Grade 2 weight loss, and Grade 1 increase in BUN. The extent of recovery was not documented.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hemorrhage: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual severe bleeding or hemorrhage.

Perforations and fistulas: Advise patients that gastrointestinal disorders such as diarrhea, nausea, vomiting, and constipation may develop during CABOMETYX treatment and to seek immediate medical attention if they experience persistent or severe abdominal pain because cases of gastrointestinal perforation and fistula have been reported in patients taking CABOMETYX.

Thrombotic events: Venous and arterial thrombotic events have been reported. Advise patients to report signs or symptoms of an arterial thrombosis. Venous thromboembolic events including pulmonary embolus have been reported. Advise patients to contact their health care provider if new onset of dyspnea, chest pain, or localized limb edema occurs.

Hypertension and hypertensive crisis: Inform patients of the signs and symptoms of hypertension. Advise patients to undergo routine blood pressure monitoring and to contact their health care provider if blood pressure is elevated or if they experience signs or symptoms of hypertension.

Diarrhea: Advise patients to notify their healthcare provider at the first signs of poorly formed or loose stool or an increased frequency of bowel movements.

Palmar-plantar erythrodysesthesia: Advise patients to contact their healthcare provider for progressive or intolerable rash.

Hepatotoxicity: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, or easy bruising or bleeding.

Adrenal insufficiency: Advise patients receiving with nivolumab to contact their healthcare provider immediately for signs or symptoms of adrenal insufficiency.

Proteinuria: Advise patients to contact their healthcare provider for signs or symptoms of proteinuria.

Osteonecrosis of the jaw: Advise patients regarding good oral hygiene practices. Advise patients to immediately contact their healthcare provider for signs or symptoms associated with osteonecrosis of the jaw.

Impaired wound healing: Advise patients that CABOMETYX may impair wound healing. Advise patients to inform their healthcare provider of any planned surgical procedure.

Reversible posterior leukoencephalopathy syndrome: Advise patients to immediately contact their health care provider for new onset or worsening neurological function.

Thyroid dysfunction: Advise patients that CABOMETYX can cause thyroid dysfunction and that their thyroid function should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of thyroid dysfunction.

Hypocalcemia: Advise patients that CABOMETYX can cause low calcium levels and that their serum calcium levels should be monitored regularly during treatment. Advise patients to immediately contact their healthcare provider for signs or symptoms of hypocalcemia.

Embryo-fetal toxicity:

- Advise females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy.
- Advise females of reproductive potential to use effective contraception during treatment with CABOMETYX and for 4 months after the final dose.

Lactation: Advise women not to breastfeed during treatment with CABOMETYX and for 4 months following the last dose.

Drug interactions: Advise patients to inform their healthcare provider of all prescription or nonprescription medications, vitamins or herbal products. Inform patients to avoid grapefruit, grapefruit juice, and St. John's wort.

Important administration information

Instruct patients to take CABOMETYX at least 1 hour before or at least 2 hours after eating.

This brief summary is based on the CABOMETYX Prescribing Information

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Use of Neoadjuvant Intravesical Therapy for Non-Muscle Invasive Bladder Cancer

By David Ambinder, MD

IS THERE A ROLE FOR neoadjuvant intravesical therapy in the treatment of patients with non-muscle invasive bladder cancer (NMIBC)? According to a recent phase 2 trial published in the *Journal of Urology,* there may be.[1] The current standard for the management of NMIBC is transurethral resection of bladder tumor (TURBT) followed by the instillation of intravesical bacille Calmette-Guérin or a chemotherapy-based agent.[2] The authors note that recurrence rates vary but range from 15% to 61% at 1 year and 31% to 78% at 5 years.[3] Recurrence of NMIBC is typically attributed to 4 mechanisms, including incomplete resection, tumor cell reimplantation, microscopic tumor growth, and new tumor formation.[4] By administering immediate single-dose intravesical chemotherapy, there is a 15% absolute risk reduction in tumor recurrence (5).5 Intravesical mitomycin-C (MMC) has a generally good systemic toxicity profile due to poor systemic absorption across the urothelium; however, the authors caution that its potential systemic toxicities should not be ignored. There have been some studies evaluating the use of MMC in the neoadjuvant setting, but many aspects of its use in this context, including dosing and scheduling, remain unknown. The purpose of this study was to assess the feasibility and potential efficacy of 2 doses of intravesical MMC administered 1 day and 4 hours prior to TURBT.

The study was designed as an open-label prospective, single-center, parallel-group, randomized phase 2 clinical trial over a 4-year period.

The study was designed as an open-label prospective, single-center, parallel-group, randomized phase 2 clinical trial over a 4-year period. Patients included in this study had previous cystoscopy with evidence of bladder tumors. The primary endpoint was to compare the recurrence-free survival (RFS) of those who underwent 2 doses of neoadjuvant intravesical MMC with those who underwent TURBT alone. In the MMC cohort, patients received instillation of MMC 40 mg at 1 day and 4 hours before undergoing TURBT. MMC was instilled via an 8-Fr urethral catheter and left in place for 1 to 2 hours. Following this, patients underwent surveillance and further intervention in line with the recommendations of the European Association of Urology, American Urological Association, or Society of Urologic Oncology guidelines for NMIBC. RFS was defined as the time between TURBT and the date of first positive pathology. Secondary endpoints included progression-free survival and adverse events (AEs) attributed to treatment.

A total of 99 patients were initially included in the study and randomly assigned to neoadjuvant intravesical MMC plus TURBT (intervention arm) or TURBT alone (control arm) in a nearly 1:1 ratio. After application of the exclusion criteria, 71 patients were included in the study: 33 in the intervention arm and 38 in the control arm. More than 85% of patients had a follow-up of at least 10.4 months. Patients were well-balanced between the 2 cohorts. The median time of follow-up was 36 months for the intervention arm versus 26 months for the control arm, and the median age was 65 years in the intervention group versus 70 years in the control arm. The control arm had a higher incidence of multiplicity multifocal tumor burden at 63% compared to 46% for the intervention arm. The authors used a per-protocol analysis and reported incidence of recurrence in 3 patients who underwent neoadjuvant intravesical MMC intervention arm compared with 8 in the control group, translating into an RFS rate of 97% versus 89%. No patients in the intervention group experienced recurrence compared with 3 patients in the control cohort. Additionally, 15% of patients who received neoadjuvant intravesical MMC experienced a grade 1 or 2 drug-related AE, specifically urinary frequency (9.1%) and hematuria 6.1%). There were no allergic reactions, systemic toxicities, or grade r3 or AEs reported.

The authors began their discussion by emphasizing that the standard of care—an immediate single dose of

intravesical MMC after TURBT—is generally well tolerated and reduces recurrence by 25% to 38%. However, they noted that given that following TURBT there may be areas of thinned muscularis propria in areas of deep resection, there is a risk for extensive "MMC-induced transmural necrosis/ulceration" that can result in secondary perforation. For this reason, a single immediate intravesical instillation of MMC should not be used in certain cases, including extended or deep resection or suspected bladder perforation, because extravasation of MMC into the subperitoneal or intraperitoneal space and perivesical fat necrosis may be so significant as to require intensive care monitoring, surgical debridement, and cystectomy.

This study did not address the optimal timing and interval of neoadjuvant intravesical MMC administration. In this study, patients were hospitalized 1 day in advance of TURBT and given the maximum dose of 50 mg/20 mL, followed by a second dose 4 hours before TURBT. Effective delivery was demonstrated by confirmed measurements of MMC in tumor tissue.

Kyle Rose, MD said caution should be exercised when generalizing the findings of the study since its patients were admitted the day before undergoing TURBT, which may not reflect standard practice.

The study lends evidence that neoadjuvant intravesical MMC can reduce the risk of post-TURBT intravesical instillation of MMC. The authors note that these findings are consistent with the PRECAVE randomized control trial interim analysis, which showed an 80% reduction in the risk of early recurrence for patients who received neoadjuvant intravesical MMC compared with patients who did not receive any neoadjuvant or adjuvant therapy.[6] Regarding recurrence or progression, although the study reported decreased recurrence and progression in the intervention arm, it was not sufficiently powered to fully analyze its potential benefits.

Limitations of this single-center, randomized phase 2 clinical trial include its small patient population and lack of an arm for standard of care of immediate post-TURBT intravesical MMC. Although the study demonstrated a safe profile for neoadjuvant intravesical MMC, the authors cited a significant need for a "prospective, phase III, large-scale, long-term follow-up, multicenter trial comparing neoadjuvant MMC versus a single immediate post-TURBT intravesical MMC group, especially for patients with intermediate or high risk NMIBC."[1]

The article was accompanied by several editorial comments. Woodson Smelser, MD, from Washington University in St. Louis, made the point that the study was performed before approval for gemcitabine in South Korea, where it was conducted. Dr Smelser quotes the findings of the SWOG S0337 trial that gemcitabine is less caustic, safer to handle, and typically more cost-effective than MMC[7] and may impact whether the use of neoadjuvant intravesical MMC is likely to dramatically shift the current standard of care. However, given the comfort that urologists have with intravesical MMC, it may be worthwhile to add it to the management of NMIBC. Kyle Rose, MD, from the H. Lee Moffitt Cancer Center, largely agreed with Dr. Smelser and added that caution should be exercised when generalizing the findings of the study since its patients were admitted the day before undergoing TURBT, which may not reflect standard practice.

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Upfront Cytoreductive Nephrectomy for Metastatic Renal Cell Carcinoma Treated With Immune Checkpoint Inhibitors or Targeted Therapy—An Observational Study

By David Ambinder, MD

IT IS TIME FOR AN UPDATE on the ever-changing landscape of the use of cytoreductive nephrectomy for metastatic renal cell carcinoma (RCC) in the era of immunotherapy. In a recent retrospective study from the Dana-Farber Cancer Institute and Harvard Medical School, Bakouny et al presented data from the International Metastatic RCC Database Consortium (IMDC). The findings address the role of upfront cytoreductive nephrectomy for patients with metastatic RCC who are treated with immune checkpoint inhibitor (ICI) or targeted therapy.[1]

The authors began by detailing the historical data that underlie the controversy around the role of cytoreductive nephrectomy for metastatic disease. At a time when patients with metastatic RCC were being treated primarily with interferon-based therapy, several studies reported consistent improved overall survival (OS) results when patients received cytoreductive nephrectomy in addition to systemic therapy.[2,3] By contrast, the CARMENA trial found that in patients with intermediate- and poor-risk metastatic disease, the addition of cytoreductive nephrectomy to sunitinib yielded no improvement in OS.[4] However, a subgroup analysis stratifying patients using IMDC criteria[5] and other retrospective studies have demonstrated a benefit with cytoreductive nephrectomy.[6] Importantly, the standard of care for the management of metastatic RCC has changed since many of these studies were conducted; the disease is now managed primarily with ICIs. In their study, Bakouny et al sought to evaluate the benefit of upfront cytoreductive nephrectomy in the age of targeted or ICI-based therapies.

The IMDC is a prospectively maintained database of patients with metastatic RCC and was reviewed retrospectively in this study. The authors noted 3 important criteria for inclusion in the database. Patients had to be diagnosed with de novo RCC or had to not have received a nephrectomy for localized RCC. Patients had to have been treated with a first-line ICI or targeted therapy, and first-line systemic therapy had to be initiated on or after January 2009. Patients were divided into 2 cohorts based on whether they had received an ICI or systemic therapy and were subdivided based on whether or not they had undergone upfront cytoreductive nephrectomy. The primary outcome investigated in the study was OS. Multivariable logistic regression models were used to identify predictor variables to ascertain whether patients were more or less likely to undergo cytoreductive nephrectomy.

A total of 4639 patients met the eligibility criteria, of whom 4202 were treated with targeted therapy and 437 were treated with ICIs. Of patients who underwent targeted therapy, 62% had been treated with sunitinib, and 50% of patients who received ICI therapy had been treated with a combination of nivolumab and ipilimumab. Additionally, 55% of patients in the targeted therapy group and 54% of those in the ICI group had received an upfront cytoreductive nephrectomy. The authors note that after undergoing cytoreductive nephrectomy, the median time to initiation of systemic therapy was 3.1 months for the targeted therapy cohort and 2.5 months for the ICI cohort. For patients who had received cytoreductive nephrectomy, the mean age was 60 years in the ICI cohort and 61 years in the targeted therapy cohort, whereas it was 63 years in both cohorts for patients who did not receive cytoreductive nephrectomy. The authors noted that "the IMDC prognostic profiles of patients who received cytoreductive nephrectomy were better in both treatment groups, with 72% and 60% of the patients belonging to the intermediate risk group in the immune checkpoint inhibitor and targeted therapy groups, respectively, as compared with 47% and 46% who did not receive cytoreductive nephrectomy, respectively."[1] On multivariable logistic regression analysis, older age (r65 years), the presence of metastasis involving bone, brain, or

liver, a low Karnofsky performance scale score (<80), and poor IMDC risk factors were associated with less likelihood of undergoing cytoreductive nephrectomy.

Bakouny et al also evaluated the relationship between receiving cytoreductive nephrectomy and OS. There were 2927 deaths reported in the targeted therapy group and 123 deaths in the ICI group. For surviving patients, the median follow-up time was 24 months for the targeted therapy group and 12 months for the ICI group. Median OS for patients in the ICI group was 54 months (95% CI, 34-not reached) for those who received cytoreductive nephrectomy versus 22 months (95% CI, 17-25) for those who did not; in the targeted therapy group, the median was 25 months (95% CI, 23-26) for those who received cytoreductive nephrectomy versus 13 months (95% CI, 12-14) for those who did not. These findings were consistent when accounting for multiple confounding variables showing an OS benefit for patients who underwent an upfront cytoreductive nephrectomy in both the ICI (hazard ratio [HR], 0.61; 95 CI, 0.4-0.9; P=0.013) and targeted therapy (HR, 0.72; 95% CI, 0.67-0.78; *P*>0.001) cohorts. Of note, there was no detectable significant difference between the 2 cohorts in the survival benefit received from an upfront cytoreductive nephrectomy. The authors then challenged their findings by considering both recognized and unrecognized confounders and found consistent results showing a survival benefit.

Bakouny et al found that "upfront cytoreductive nephrectomy was associated with a significant survival benefit, regardless of the systemic therapy used even after adjusting for potential confounding factors."

Bakouny et al found that "upfront cytoreductive nephrectomy was associated with a significant survival benefit, regardless of the systemic therapy used even after adjusting for potential confounding factors."[1] In this study, patients were more likely to receive an upfront cytoreductive nephrectomy if they were younger in age, had fewer IMDC risk factors, had a better Karnofsky performance status, and had no adverse sites of metastasis such as bone, brain, or liver. The findings suggest that, in this era of ICI-based therapy, patients who are carefully selected and meet these criteria may benefit from upfront cytoreductive nephrectomy—a benefit the authors speculate could "be due to the immune effects of cytoreductive nephrectomy."[7] The idea behind this is that primary RCC tumors may release cytokines that promote inflammation and inhibit T cells, which could impede the systemic antitumor immune response.[8] Bakouny et al concluded that "the removal of the primary tumor may be potentiating a more effective immune response mounted against the metastatic RCC lesions treated with immune checkpoint inhibitors."[1]

The findings of improved OS with cytoreductive nephrectomy in patients treated with immunotherapy are consistent with results from other recently published studies.[9,10] This study's strength lies in being a multicenter, large study that performed analyses incorporating potential confounders. However, its limitations include that it was a retrospective, nonrandomized study that did not include all the potential confounders that might have influenced whether a patient received a cytoreductive nephrectomy, and it was largely conducted in an academic cohort that was not necessarily representative of the general population. Nevertheless, in the absence of randomized controlled trials, these findings may help guide clinicians in determining which patients would most benefit from undergoing a cytoreductive nephrectomy.

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5-Year Outcomes After Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma—An Individual Patient Data Meta-Analysis from IROCK

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WHAT CAN WE OFFER patients with primary renal cell carcinoma (RCC) who are unable to undergo surgery? According to a recent study published in *The Lancet Oncology*, radiation may be an answer offering safety and long-term efficacy.[1] This report has particular relevance for elderly patients. The authors begin by noting that the incidence of RCC is rising especially in patients older than 70 years. These patients typically have more comorbidities, putting them at increased risk for surgical intervention. Current guidelines recommend that for these patients, thermal ablation, and stereotactic ablative body radiotherapy (SABR) are potential options.[2] The utilization of SABR has been increasing,[3] and support for its use include efficacy and safety results in in several studies[4,5,6]; however, long-term follow-up data have been lacking. This is what propelled the authors of the current study to assess the long-term data for use of SABR in patients with primary RCC from the International Radiosurgery Oncology Consortium of the Kidney (IROCK). The population included patients with long-term follow-up and additional patients registered from contributing institutions.

The study included patients from 5 countries including the United States at 12 international institutions over an 11-year period between 2007 and 2018. Patients were included only if they were followed for r2 years, were diagnosed with nonmetastatic RCC at the time of diagnosis, were adults with any performance status, and had no contraindications for receiving SABR. Specific excluded patients were those with previous abdominal radiation or a previous diagnosis of upper tract urothelial carcinoma. All patients were considered inoperable by the referring urologist.

Patients were followed every 3 to 4 months in year 1, every 3 to 6 months in years 2 and 3, and every 6 to 12 months after year 3 using computed tomography imaging and serum creatinine. According to the authors, "The primary objective of this study was to assess the local efficacy of SABR for primary renal cell carcinoma and secondary objectives were to evaluate treatment related toxic effects, patterns of failure, survival, and renal function outcomes."[1] Survival endpoints included progression-free survival (PFS), cancer-specific survival (CSS), local failure, distant failure, and any failure.

Nearly 200 patients were included in the study with a median age of 73.6 years; the median follow-up time was 5 years. A total of 73% of patients were men and 27% were women. Overall, 88% of patients had good performance status measured by an Eastern Cooperative Oncology Group (ECOG) score of 0 to 1, or a Karnofsky performance status score of r70%. 83% of patients had biopsy confirmed RCC. Baseline tumor complexity was moderate as measured by the R.E.N.A.L. nephrometry score (R=radius [tumor size as maximal diameter], E=exophytic/endophytic properties of the tumor, N=nearness of tumor deepest portion to the collecting system or sinus, A=anterior [a]/posterior [p] descriptor, L=location relative to the polar line). Nearly 30% of patients had only 1 kidney. Of note, no patients included in the study received adjuvant or concurrent systemic therapy. Local failure was 5.5% at 3 years, 5.5% at 5 years, and 8.4% at 7 years; 86% of patients did not have a recorded failure. A total of 35% of patients died during the follow-up period. In 15% of those patients, deaths were attributed to cancer-related causes and 77% were attributed to nonmalignant causes, including cardiovascular causes (18%).

Other causes of death included sepsis, renal failure, respiratory failure, acute subdural hemorrhage, liver disease, lung disease, and pneumonitis. There were 5 patients who died from other malignancies. CSS was 95.5% at 3 years, 92% at 5 years, and 92% at 7 year and the progression free survival at 3 years, 5 years and 7 years was 72.1%, 63.6%, and 48.5% respectively. Median PFS was 6.7 years (95% CI, 5.5-7.5). The 3-year, 5-year, and 7-year estimates from local failure were 93.7%, 93.7%, and 89.4% respectively, while the 3-year, 5-year and 7-year estimates of freedom from distant failure was 90.5%, 87.3%, and 81%, respectively,

indicating that the dominant pattern of progression was distant failure. The endpoint of median times to any failure was not reached. The authors note that "1 of 4 patients with local progression underwent successful salvage with radical nephrectomy, whereas the remaining 3 were not considered for surgery due to either pre-existing medical inoperability or T4 disease, which was surgically inoperable."[1]

The authors then evaluated the effects of SABR on renal function. Chronic kidney disease (CKD) classification before and after SABR remained stable in nearly half the patients and worsened in 47%; 7% declined to end-stage renal failure and renal function improved in 5%. For almost all patients, the median baseline estimated glomerular filtration rate (eGFR) was 60 mL/min per 1.73 m^2. Median eGFR was reduced by 5.5 at 1 year, 10.3 3 years, and 14.2 at 5 years. A similar trend seen for creatinine, with results showing an inverse steady increase in creatinine. A total of 4% of patients underwent dialysis after receiving SABR.

In all, 50% of patients had tumors <4 cm (median 2.8 cm) and 50% had tumors >4 cm (median 4.9 cm). The authors noted that patients with tumors r4 cm were more likely to be older, with worse performance status, and underwent less total radiation dosing. Importantly, there was no difference in CSS, PFS, or local or distant failure between patients with tumors <4 cm and patients with tumors >4 cm. The cumulative incidences of local failure were 4.2 versus 6.7% in the <4 cm versus >4 cm groups, and the corresponding 5-year estimates of freedom from local failure were 95.4% versus 92%. The authors then investigated whether tumor complexity is associated with treatment-related toxic effects, worsening eGFR, and local failure. They found an association with tumor complexity as measured by the R.E.N.A.L. nephrometry score and treatment-related toxic effects, as well as large declines in renal function (at 3 and 5 years, but not at 1 year), while there was no association appreciated with local failure.

When comparing patients with 1 kidney as compared to those with 2 kidneys, patients had better performance status, were younger, had a higher proportion of clear cell histology, and received lower total radiation in fewer fractions. Of the patients with 1 kidney, 75% underwent single-fraction SABR and 2 patients required dialysis. No significant difference in decline in eGFR was observed when compared patients with 1 versus 2 kidneys. There also was no difference in CSS, PFS, or local or distant failure.

Single-fraction SABR was delivered in 43% of patients at a median dose of 25 Gy, while multifraction SABR was administered in the other 57% of patients at a median dose of 42 Gy in 2 to 10 fractions over a median of 7 days. No significant difference in the incidence of toxicity events was seen. Patients who underwent single-fraction SABR were younger, had better performance status, and were more likely to have clear cell histology and a solitary kidney. Patients who underwent single-fraction SABR had reduced rates of local failure and experienced improvement in PFS but not CSS. Multivariable analysis showed a significantly higher risk of local failure for patients who received multifraction SABR (hazard ratio [HR], 6.10; 95% CI, 1.02-36.66; P=0.048) but not distant failure.

Grade 1 to 2 toxicities were seen in 37% of patients, but there were no grade 3 events. One patient had a grade 4 duodenal ulcer and late grade 4 gastritis.

This study is the first to describe long-term outcomes with a median of 5 years for use of SABR in patients with primary RCC. This study showed a 5.5% 5-year local failure rate and a 5-year CSS rate of 92% in a population that was considered to be inoperable. The authors observed a significant difference in PFS and local failure between single-fraction and multifraction SABR, and on multivariable analysis, there was still a significantly higher risk of local failure for multifraction SABR compared with single-fraction SABR. The authors also found no difference in long-term renal function outcomes in the single fraction versus multifraction cohorts. The authors note that these results comparing single fraction and multifraction SABR should be interpreted with caution and are not definitive, but should be treated as hypothesis generating. They noted that these findings will be evaluated in a "prospective randomized registry trial, with the infrastructure for the IROCK registry under development."[1]

The finding in this study that patients with smaller renal masses had a 95.4% 5-year survival with freedom from local failure is consistent with other studies.[7] Limitations of the study included possible underreporting of treatment-related toxic effects. Nevertheless, the authors concluded that "this analysis provides mature outcome and safety data for SABR in primary renal cell carcinoma. Single fraction SABR yielded fewer local failures than multifraction SABR. This observation should be tested in a prospective randomized trial.[1]

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Comparison of Analgesic Modalities for Minimally Invasive Surgery

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UROLOGIC CANCERS CONSISTING of prostate cancer, bladder cancer, and kidney cancer are 3 of the top 10 malignancies in the United States.[1] Annually, ~90,000 cases of prostate cancer are treated surgically, with most using minimally invasive robotic approaches.[2] For bladder cancer, only an esitmated 1 of 5 patients will receive this curative procedure.[3] Patients who receive this curative treatment are increasingly receiving treatment via minimally invasive techniques as more clinical trial data emphasize its benefits.[4] In the realm of kidney cancer, an estimated 6000 partial nephrectomies are completed in the United States annually with a continued trend toward minimally invasive modalities.[5] Although utilization of minimally invasive radical nephrectomy has declined with higher rates of suiccessful partial nephrectomy, a sizable number of patients still also undergo laparoscopic or robotic partial nephrectomy.[6] As rates of cancer diagnoses continue to increase, the quantity of minimally-invasive procedures conducted to treat these malignancies is expected to increase in volume. In this brief review, we detail the analgesic modalities avaliable for treatment of patients undergoing minimally-invasive urologic surgery.

Analgesic options can be broadly classified into oral nonopioid classes such as nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 inhibitors (COX-2), oral opioids, gabapentin, and local techniques such as transversus abdominus plane (TAP) blocks. As the now predominant modality, we will reference pain management for patients undergoing robot-assisted procedures. Most patients undergoing robot-assisted radical prostatectomy (RALP) report mild to moderate levels of pain.[7] Similar findings can be seen with partial nephrectomy, with patients undergoing treatment with laparoscopic or robotic approaches reporting pain scores on the lower analog pain scales (average score <3).[8] Evidence for use of NSAIDs in minimally invasive surgery comes from several trials primarily conducted in the open radical prostatectomy setting. A meta-analysis comparing prominent NSAIDs such as diclofenac and parecoxib with placebo reported that pain scores generally decreased and requirements for additional pain control also decreased.[9]

COX-2 inhibitors, a subclass of NSAIDs, are another important class of medication important in this context. COX-2 inhibitors function by inducing reversible inhibition of either COX-1 or COX-2. Aspirin, for example, is a nonselective inhibitor of both targets, whereas celecoxib, which is commonly used for pain control, specifically targets COX-2. Chelly et al conducted a study comparing celecoxib in a multimodal analgesic approach to patient-controlled morphine anesthesia.10 The authors reported a decline of slightly greater than 50% in the need for morphine in the multimodal analgesia arm.[10] Similar findings were seen in a similar study comparing rofecoxib to placebo.[9]

Gabapentin is another commonly used medication class in the postoperative setting. The exact mechanism of action for gabapentin is unknown, but it is thought to act by inhibiting calcium channels. It is commonly used in the treatment of postherpetic neuralgia, restless legs syndrome, and partial seizures.[11] Off-label it can be used for neuropathic pain. Deniz et al investigated the use of gabapentin in a patient population undergoing radical prostatectomy.[12] Patients receiving a 900-mg dose of gabapentin preoperatively demonstrated a lower perception of early postoperative pain compared with patients who did not. However, total opioid pain medication consumption (tramadol in this instance) was found to be similar between the groups. This suggests that gabapentin may play a useful role in the same-day surgery setting. By reducing early postoperative pain scores, patients may feel more comfortable being discharged the same day with home pain regimens.

Opioid-based medications are generally regarded as less than ideal for primary pain management because of their class-related side effects that have been shown to delay return of bowel function and to induce bowel-related symptoms such as nausea or emesis. The recently updated expert consensus panel statement published in *Journal of Urology* recommends that "Patients should maximize nonopioid agents, including acetaminophen and nonsteroidal anti-inflammatory drugs, for baseline pain control unless contraindicated."[13] For all laparoscopic and robot-assisted procedures, the consensus statement

suggests that patients maximize analgesic control with nonopioid agents such as acetaminophen and other NSAIDs.[13] The statement recommends up to 15 doses of oxycodone 5 mg, or the equivalent, for discharge.[13]

While instillation of local anesthetic at port sites is a commonly used technique, it is worthwhile for clinicians to become familiar with some of the advanced modalities, such as continuous infusion and TAP blocks. In a placebo-controlled trial, Kristensen et al reported on the subject of local wound infusion with bupivacaine following prostatectomy.[14] The goal of this technique was to improve postoperative pain control by continuous infusion of a subfascial-placed catheter for 48 hours after surgery to reduce total opioid (morphine) requirements. The authors reported that patients in the placebo arm required higher doses of morphine in the early postoperative setting; however, overall, there was no significant difference in the amount of morphine required between the 2 groups.

As larger volumes of patients are diagnosed with localized prostate, kidney, or even bladder cancer, it is crucial for clinicians to understand postoperative pain control regimens to facilitate earlier return to activities of daily life and promote earlier discharge.

TAP blocks are also commonly used after urologic surgery. Unlike some of the modalities mentioned earlier, TAP blocks have been shown in randomized trials to overall lower pain scores and lower opioid requirements. TAP blocks function by inhibition of sensory afferents along the anterior abdominal wall (T7-L1).[15] Elkassabany et al conducted a randomized trial comparing patients who underwent TAP block with bupivacaine versus control (normal saline).[15] Patients in the TAP arm reported overall lower pain scores and lower opioid usage over the initial 24 postoperative hours; however, they note that these effects were more prominent in the first 6 postoperative hours, suggesting that such blocks may be similarly useful for same-day discharge protocols.

Other creative modalities for pain control have also been attempted. For example, Weinberg et al reported on the use of dorsal penile nerve blocks after RALP.[16] The authors randomized patients to bupivacaine dorsal penile nerve block or placebo, but the results showed no significant difference in catheter discomfort or narcotic utilization between the 2 groups.[16]

As larger volumes of patients are diagnosed with localized prostate, kidney, or even bladder cancer, it is crucial for clinicians to understand postoperative pain control regimens to facilitate earlier return to activities of daily life and promote earlier discharge. The studies referenced in this article focus on treatment of localized prostate cancer, but similar findings can be seen across the literature for all minimally invasive abdominal surgical procedures.

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Postprostatectomy Radiation Highlights

Akhil A. Saji, MD

MANY PATIENTS DIAGNOSED with localized prostate cancer will undergo primary therapy with radical prostatectomy. An estimated 25% to 40% of such patients will eventually experience biochemical recurrence (BCR) by 10 years after primary therapy.[1,2] Postprostatectomy patients with BCR may be offered salvage radiation therapy if they have a rising detectable prostate-specific antigen (PSA)level and no radiographic evidence of nodal or metastatic disease. At the American Society for Radiation Oncology (ASTRO) 2022 meeting, several authors presented abstracts on the topic of postprostatectomy radiation that are worth reviewing.

The NRG Oncology Group presented a timely abstract article entitled "The Influence of Pelvic Node Dissection Volumes on Clinical Outcomes in NRG/RTOG 0534." RTOG 0534 was a phase 3 randomized, multicenter, clinical trial investigating the role of short-term androgen-deprivation therapy (ADT) or lymph node radiation therapy in treatment of patients receiving salvage prostate bed radiation therapy for BCR.[3] Between March 2008 and March 2015, the authors of the study enrolled 1792 patients into 3 arms: prostate bed radiation alone (arm 1; control), prostate bed radiation plus short-term ADT (arm 2), and prostate bed radiation plus short-term ADT and lymph node radiation (arm 3). At the interim analysis, results reported in *The Lancet* demonstrated that addition of short-term radiation and pelvic lymph node radiation to prostate bed radiation improved 5-year freedom from progression compared with prostate bed radiation alone ($P<0.0001$). At ASTRO 2022, William A. Hall, MD, addressed another observation of this trial—the high variation in pelvic lymph node dissection volumes at the time of radical prostatectomy.

According to Dr. Hall, it has often been hypothesized that the volume of lymph nodes removed at the time of prostatectomy may affect the benefit the patient would receive from pelvic lymph node radiation. The rationale is that patients who have more lymph nodes removed would be more accurately staged and have less lymph node volume to benefit from radiation. However, this has not been corroborated by data. In each of the 3 arms of the RTOG 0534 trial, patients had a mean range of 4.4 to 4.8 lymph nodes at the time of prostatectomy, indicating relative similarity between the cohorts. However, Dr. Hall also noted that a sizable portion of patients had no nodes removed (37%). In the abstract presented at ASTRO, the NRG group sought to evaluate the influence of pelvic lymph node dissection volumes on clinical outcomes.[4] The primary outcomes of interest were freedom from progression, evaluation of toxicity, and development of distant metastatic disease. Using data from RTOG 0534, the authors constructed multivariable Cox proportional hazard models to evaluate these outcomes with dissection of 0 to 1 lymph nodes versus dissection of ≥2 nodes.

Descriptive analytics of the study population revealed some interesting trends. Dr. Hall remarked that patients with higher Gleason grade scores tended to have greater numbers of lymph nodes resected (Gleason grade 7; 66% of patients ≥2 lymph nodes). Additionally, patients with higher stage disease (cT3) and seminal vesicle involvement had higher rates of more aggressive lymph node dissection. Interestingly, patients who received pelvic lymph node dissection at academic centers had higher rates of more aggressive lymph node dissection (≥2 lymph nodes; 84.4%) compared with those treated at community hospitals (15.6%). The hazard models produced by the authors demonstrated that when comparing arm 1 and arm 3 for patients with ≥2 lymph nodes resected, there was 140% benefit (hazard ratio [HR], 2.4 in arm 1 vs 1.8-3.19 in arm 3), demonstrating that the volume of original lymph node dissection does not appear to affect the therapeutic potential of lymph node radiation. Conducting the same analysis for development of distant metastases, the authors demonstrated that patients with 0 to 1 lymph nodes resected received the greatest oncologic benefit from addition of short-term ADT and lymph node radiation, and the benefit decreased linearly as the number of nodes dissected increased. In concluding remarks, Dr. Hall summarized that for freedom from disease progression, no difference was seen between arm 2 and arm 3, but the results also suggested that

patients with larger quantities of lymph nodes resected at prostatectomy may benefit more from lymph node radiation. Regarding development of distant metastasis, the multivariate analysis suggested that patients with ≥2 lymph nodes removed did not benefit from pelvic lymph node radiation.

A second interesting phase 2 trial on the topic of postprostatectomy radiation therapy investigated the role of enzalutamide in salvage radiation therapy after radical prostatectomy. Phuoc Tran, MD, PhD, presented results from the SALV-ENZA trial, a phase 2 randomized trial of salvage radiation therapy plus either enzalutamide or placebo in high-risk patients with PSA recurrence after radical prostatectomy for prostate cancer.[5] Enzalutamide is a third-generation nonsteroidal androgen receptor antagonist approved for use in patients with metastatic castration-resistant prostate cancer or metastatic hormone-sensitive prostate cancer. There has been widespread interest in employing enzalutamide in other clinical scenarios such as BCR, which the SALV-ENZA trial intends to investigate.

Dr. Tran emphasized that the phase 2 data are promising, and the benefit should be further explored in a phase 3 trial.

Dr. Tran remarked that several trials have demonstrated the benefit of adding ADT to salvage radiation therapy for patients with BCR; however, ADT is not benign. He explained that patients receiving ADT often experience several adverse events, including metabolic syndrome, erectile dysfunction, lower quality of life, and decreases in bone mineral density. In comparison, Dr. Tran explained that patients receiving enzalutamide in this setting have stable rates of bone mineral density, improved quality of life, and stable metabolic profiles. Therefore, the authors of the trial made the case that enzalutamide, when compared with traditional ADT, may be better for patients undergoing salvage radiation therapy for BCR after prostatectomy.

The authors enrolled 86 patients (162 screened) who had received prostatectomy for high-risk prostate cancer and had experienced evidence of recurrence. Specifically, patients enrolled had either Gleason grade 7 disease with an advanced clinical stage (cT3 or positive margins) or Gleason grade 8 to 10 disease. Patients were randomized into 2 arms of salvage radiation plus placebo or salvage radiation plus enzalutamide. The primary endpoint sought by the trial was freedom from PSA progression.

Dr. Tran depicted the results of the trial on a Kaplan-Meier curve showing the probability of freedom from PSA progression. Overall, patients in the experimental (enzalutamide) arm demonstrated significant (58%) benefit regarding freedom from PSA progression compared with those who received placebo (HR, 0.42; *P*=0.027). Furthermore, Dr. Tran remarked that at 24 months, there was an 18% difference in freedom from PSA progression between the 2 arms. The subcohort analysis also demonstrated interesting results. Dr. Tran remarked that patients with positive margins and T3 disease likely received the most benefit. The subcohort analysis also showed that nearly all patients benefited to some extent, with most HRs between 0.25 to 0.90. In terms of the toxicity profile with addition of enzalutamide, Dr Tran remarked that, overall, the therapy was well tolerated with few grade 3 complications (3 total). Most toxicity was grade 1 to 2, with 18.7% of patients experiencing nausea and 25.6% experiencing breast pain and tenderness.

In concluding, Dr. Tran noted that one of the limitations of the SALV-ENZA trial was the use of freedom from PSA progression instead of overall survival (OS) as an endpoint, and stated that future studies must address OS. He also remarked that the data provided in this phase 2 trial give credence to the utility of enzalutamide monotherapy with salvage radiation therapy for BCR in patients after radical prostatectomy. He emphasized that the phase 2 data are promising, and the benefit should be further explored in a phase 3 trial.

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ASTRO 2022 Science Highlights

Akhil A. Saji, MD



THIS YEAR'S ANNUAL MEETING of the American Society for Radiation Oncology (ASTRO 2022) included several interesting articles about genitourinary cancer. Many of them focused on prostate cancer, but there also were some on bladder cancer. Gerard Morton, MB, BCh BAO, MRCPI, FFRRCSI, FRCPC, of Sunnybrook Odette Cancer Centre at the University of Toronto highlighted a few key abstracts of interest to clinicians.

In the realm of prostate cancer, Dr. Morton explained 3 themes of questions that the abstracts at ASTRO sought to answer: (1) In primary prostate cancer, how does hypofractionated radiation therapy compare to conventional radiation therapy in high-risk patients? (2) What is the role of high- dose rate (HDR) boost in brachytherapy for prostate cancer? (3) How does HDR compare to low-dose rate (LDR) boost?

The first trial reviewed was the PCS5 clinical trial.[1] PCS5 is a phase 3 trial being conducted in Canada that focuses solely on patients with high-risk prostate cancer (stage >cT3a, prostate-specific antigen [PSA] >20, or Gleason grade 8-10) randomized to conventional or hypofractionated radiation therapy. The authors sought to evaluate early and late toxicity, as well as the secondary endpoints of overall survival (OS), disease-specific survival (DSS), distant metastases, and quality of life (QOL) factors. At the ASTRO meeting, the authors of the PCS5 trial presented data from the median follow-up of 7 years. In reviewing the patient characteristics, Dr. Morton confirmed that the trial had enrolled only patients with high-risk prostate cancer, with 49% having Gleason grade 8 disease and 34% having Gleason grade 9 to 10 disease.

Findings for the primary endpoint of the PCS5 trial demonstrated that hypofractionated primary radiation therapy was safe and noninferior to conventional radiation therapy. The authors reported similar rates of grade r2 gastrointestinal (GI) toxicity (hypofractionated vs conventional, 9% vs 8%) and genitourinary (GU) toxicity (2% vs 7%). Regarding the secondary endpoints, the authors presented Kaplan-Meier survival curves for OS and DSS that demonstrated near-identical oncologic outcomes, suggesting that hypofractionated radiation can be used safely in patients with high-risk prostate cancer. Dr. Morton remarked that the data offers support for clinicians utilizing hypofractionation in this setting.

Dr. Morton also reviewed the topic of brachytherapy by referencing the American Society of Clinical Oncology guidance that patients with intermediate- or high-risk prostate cancer should receive a brachytherapy boost.[2] At ASTRO 2022, Moideen et al presented a phase 3 trial investigating the role of HDR boost compared with LDR boost in prostate cancer brachytherapy.3 Specifically, the authors hypothesized that HDR boost would provide the same oncologic efficacy while improving QOL compared with LDR boost.

The authors enrolled 195 patients with a prostate volume <60 mL and low urinary symptom International Prostate Symptom Score (IPSS; <16) to either HDR boost or LDR boost categories. The primary and endpoints focused on QOL (Expanded Prostate Cancer Index Composite [EPIC] urinary, bowel, and sexual function scores at 6 months). Dr. Morton briefly reviewed the patient demographics of the trial cohort, which comprised primarily older patients (mean age, 71.1 years) most of whom had high-risk disease (57%). He emphasized that the sequence of intervention differed between the 2 arms, primarily in that patients in the HDR boost arm received the boost before initiation of external- beam radiation therapy (EBRT) while patients in the LDR boost arm received the implantations shortly after completing EBRT. In reviewing the results, Dr. Morton demonstrated that patients in both arms saw decreases in urinary QOL, which subsequently recovered to baseline by 12 months; however, for GI QOL, patients receiving LDR had prolonged decreases in QOL that never recovered to baseline levels. Like urinary QOL, patients had similar sexual QOL scores, regardless of the boost mechanism used. In conclusion, the data from this trial suggest that use of HDR boost facilitates improved early urinary QOL compared with LDR boost, although there is no difference later in the treatment course. HDR boost also seems to portend improved GI symptoms and QOL. Dr Morton emphasized that these findings must be taken in context considering that LDR radiation doses were overall higher and LDR has a long history of clinical efficacy that HDR boost lacks.

ASTRO 2022 also offered pertinent updates on the management of bladder cancer. The 2 primary strategies for bladder preservation in the setting of muscle-invasive bladder cancer are trimodal therapy and partial cystectomy. Trimodal therapy consists of maximal transurethral resection of the bladder tumor combined with radiosensitizing chemotherapy agents and radiation therapy. Unfortunately, there have been no direct trials comparing the outcomes in patients undergoing trimodal therapy versus standard of care radical cystectomy. Dr. Morton remarked that the SPARE trial[4] attempted to answer this question but was hampered by patient nonadherence and reluctance to agree with randomization. To simulate the outcomes of a randomized controlled trial (especially as there are no planned future randomized trials to investigate these outcomes), Efstathiou et al compiled a multi-institutional comparison of radical cystectomy versus trimodal therapy.[5]

The comparison included a sizable patient population, with 834 patients in the radical cystectomy arm and 282 patients in the trimodal therapy arm. Dr. Morton remarked that both arms had similar patient characteristics in terms of age, percentage of carcinoma in situ (CIS)-positive disease, similar clinical stage including presence of hydronephrosis, and use of neoadjuvant chemotherapy. Patients receiving trimodal therapy had a 20.5% rate of non–muscle-invasive disease recurrence and 13% required salvage cystectomy. Patients who received upfront radical cystectomy had a perioperative mortality rate of 2.1%, with most having pT3 to pT4 disease (42%) at the final pathologic analysis. Evaluation of outcomes revealed some interesting findings. All outcomes generally favored the trimodal therapy arm. At a cut point of 5 years, metastasis-free survival favored trimodal therapy over radical cystectomy (78% vs 73%) although the difference was not statistically significant (P=0.07). Evaluation of cancer-specific survival (CSS) and OS also favored trimodal therapy with a statistically significant difference for both CSS (78% vs 85%; P<0.0001) and OS (66% vs 78%; P<0.001).

Dr. Morton remarked that the results of the trial were highly unusual, particularly in demonstrating that a nonsurgical technique is potentially superior to a surgical one. He concluded by noting these are potentially the best data available, suggesting that trimodal therapy may be equivalent to or even better than radical cystectomy, with the caveat that this was not a randomized prospective trial.

The articles on prostate and bladder cancer highlighted by Dr. Morton are of key clinical interest for all practicing clinicians. The program at ASTRO 2022 included several other important and thought-provoking scientific abstracts with oncologic outcomes that are also worth reviewing.

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Prostate cancer patients with aggressive disease may require a more individualized and intensive approach to treatment

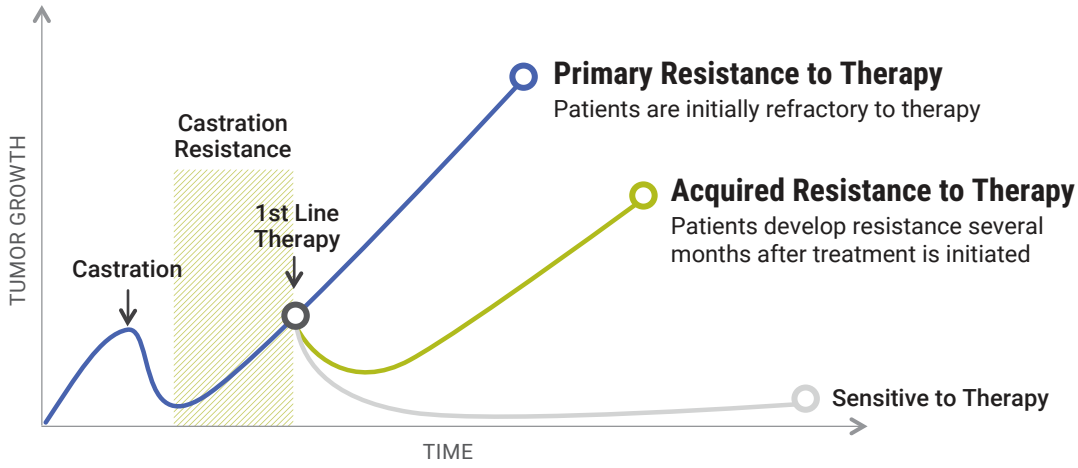
Early identification of mCRPC patients with high-volume disease is important[1,2]

Features of High-Volume Disease Include:

- **Visceral metastases**
- **Bone plus visceral metastases**
- **≥5 bone metastases**

Not all patients respond to therapy, while others lose responsiveness over time[3-5]

Therapeutic Resistance May Present in 2 Different Ways[3]:



- While prognosis is good for men with localized disease, it remains poor for men with more advanced disease[1]
- Although current therapies may slow the progression of disease, patients may experience disease progression

When deciding what's next, do you consider a patient's unique clinical factors and response to prior therapy?

To learn more visit mcrpc-treatment.com

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